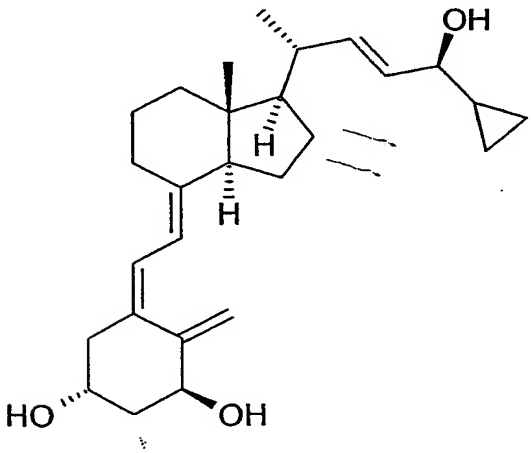
NOVEL METHOD FOR THE PREPARATION OF INTERMEDIATES USEFUL FOR THE SYNTHESIS OF VITAMIN D ANALOGUES

FIELD OF THE INVENTION

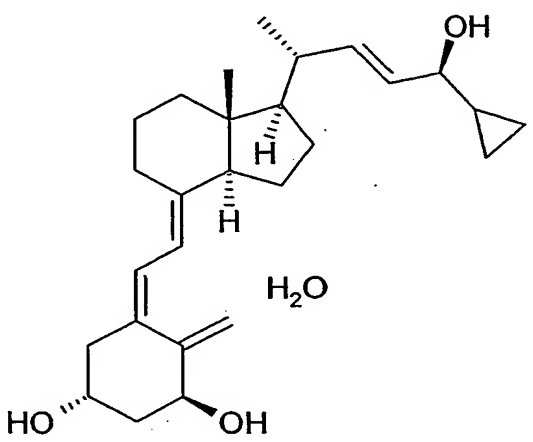
The present invention relates to novel intermediates which are useful in the synthesis of calcipotriol {(5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α-3β-24-triol} and methods for the preparation thereof. The present invention relates further to the use of intermediates produced with said methods for making calcipotriol or calcipotriol monohydrate.

BACKGROUND OF THE INVENTION

Calcipotriol or calcipotriene (structure I) [CAS 112965-21-6] shows a strong activity in inhibiting undesirable proliferation of epidermal keratinocytes [F.A.C.M. Castelijins, M.J. Gerritsen, I.M.J.J. van Vlijmen-Willems, P.J. van Erp, P.C.M. van de Kerkhof; Acta Derm. Venereol. 79, 11, 1999]. The efficacy of calcipotriol (Ia) and calcipotriol monohydrate (Ib) in the treatment of psoriasis was shown in a number of clinical trials [D.M. Ashcroft *et al.*; Brit. Med. J. 320, 963-67, 2000] and calcipotriol is currently used in several commercial drug formulations.



I

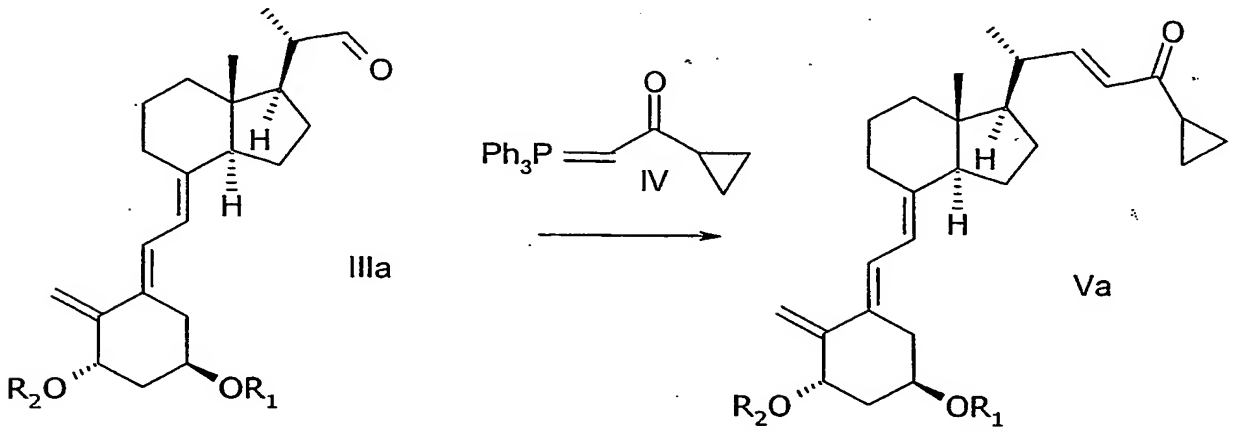


Ib

A key step in the synthesis of calcipotriol or intermediates useful for the synthesis of calcipotriol is the attachment of the cyclopropyl-enone side chain to the CD-ring of suitable precursors, which has been described with a Wittig reagent IV.

For example, in an industrial synthesis of calcipotriol, the cyclopropyl containing phosphorane side chain IV is reacted with the aldehyde IIIa in a Wittig reaction to give the enone Va, wherein R_1 and R_2 are tert-butyldimethylsilyl (see e.g. WO 87/00834 or M.J. Calverley; Tetrahedron, 43 (20), 4609-19, 1987). Calcipotriol is then obtained from

the key intermediate Va by reduction to the C-24 alcohol followed by photoisomerisation and the removal of the silyl protecting groups.

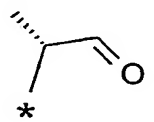


The Wittig processes using the phosphorane IV have a number of disadvantages, especially on a large scale: a) During the C=C-bond forming reaction triphenylphosphine oxide is formed as a side product which is difficult to remove from the reaction mixture. The formation of triphenylphosphine oxide currently adds an additional chromatographic step to the process outlined above. b) The Wittig reaction furthermore necessitates reaction temperatures above 95°C due to the low reactivity of the phosphorane IV. Lower reaction temperatures would be advantageous in an industrial process.

It is an object of this invention to provide an alternative process which may overcome one or more of the various problems and disadvantages described above. The present invention thus provides a novel process which can be run at lower temperature and which avoids the tedious chromatographic removal of triphenylphosphine oxide to produce intermediates useful for the synthesis of calcipotriol, such as the enone of general structure Va.

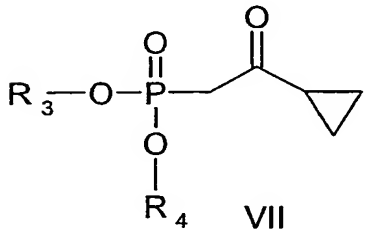
SUMMARY OF THE INVENTION

It was surprisingly found that a compound of general structure IIa,



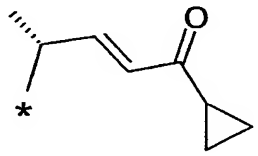
IIa

wherein the carbon marked with an asterisk is either connected by a single bond to a carbon atom of a vitamin D analogue fragment at C-17, or to a fragment of a precursor for the synthesis of a vitamin D analogue at a C-17 analogous position,
can be reacted with a phosphonate of general structure VII,



VII

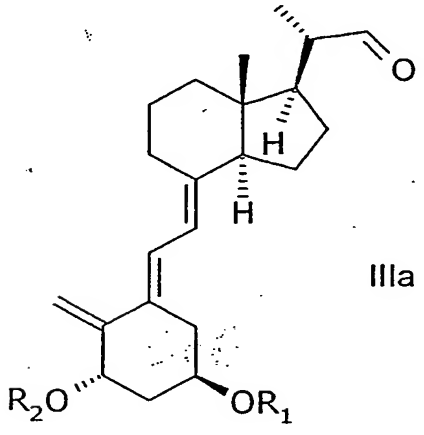
wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base,
to give a compound of general structure of general structure II,



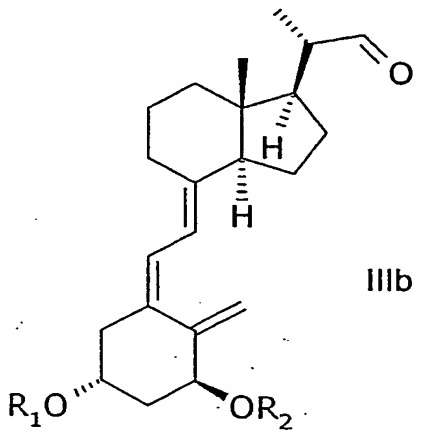
II

wherein the carbon marked with an asterisk is either connected by a single bond to a carbon atom of a vitamin D analogue fragment at C-17, or to a fragment of a precursor for the synthesis of a vitamin D analogue at a C-17 analogous position.

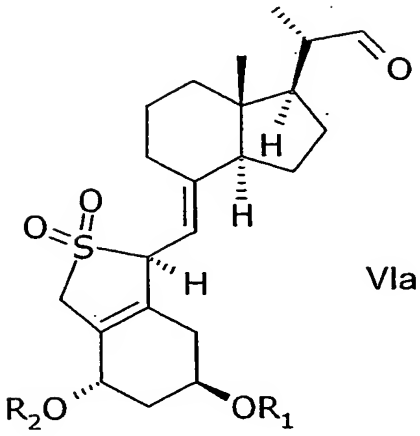
Accordingly, a compound of general structure IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, or XVb, or IXX,



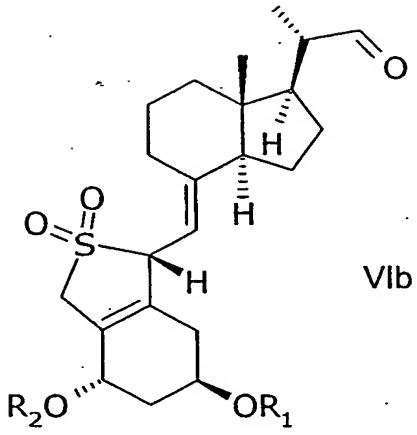
IIIa



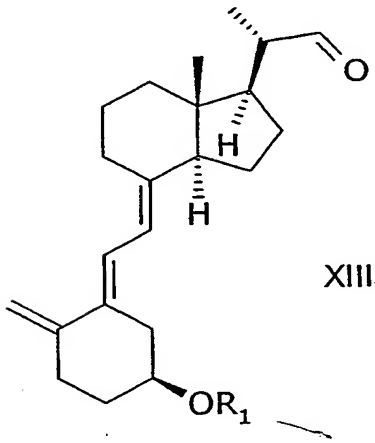
IIIb



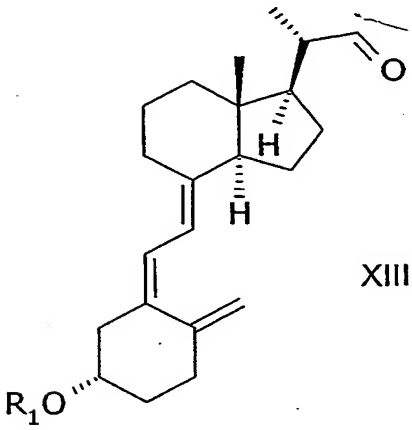
VIa



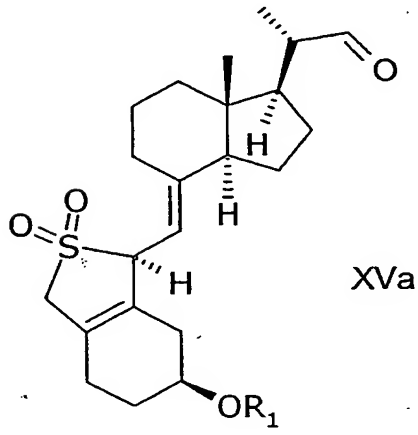
VIb



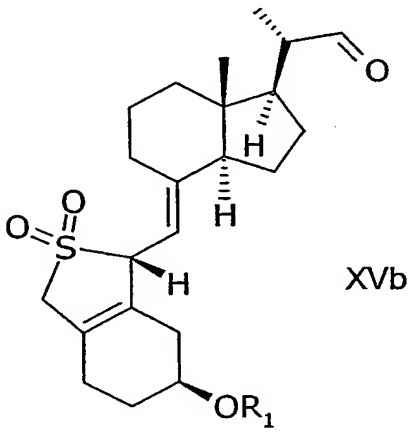
XIIIa



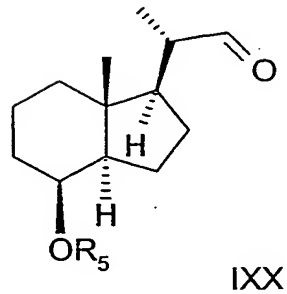
XIIIb



XVa



XVb

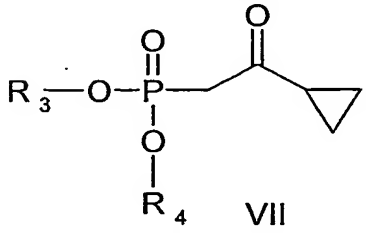


IXX

wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group,

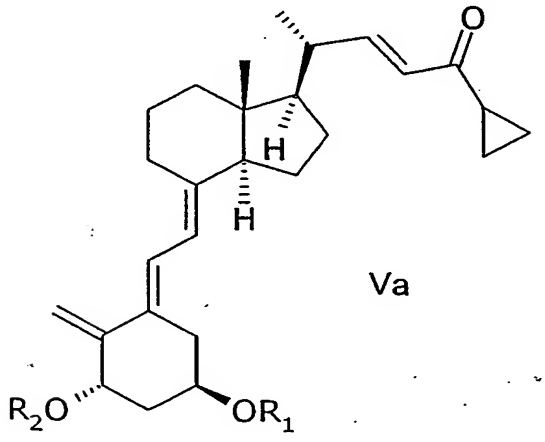
and wherein R_5 represents hydrogen or a hydroxy protecting group,

can be reacted with a phosphonate of general structure VII,

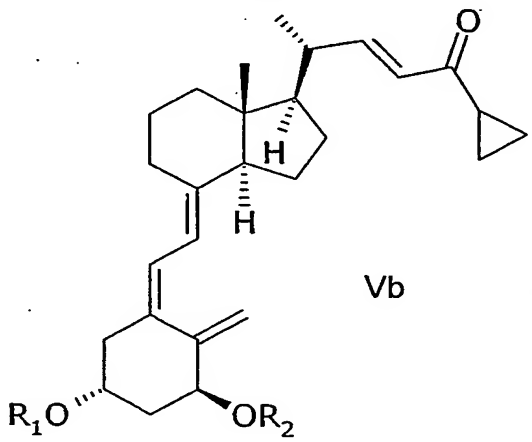


VII

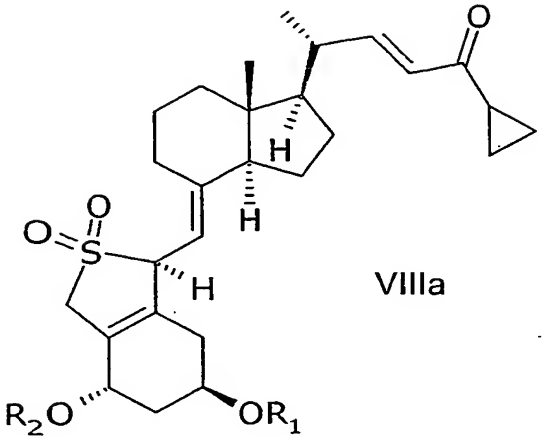
wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base, to give a compound of general structure Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, XVIb, or XX respectively,



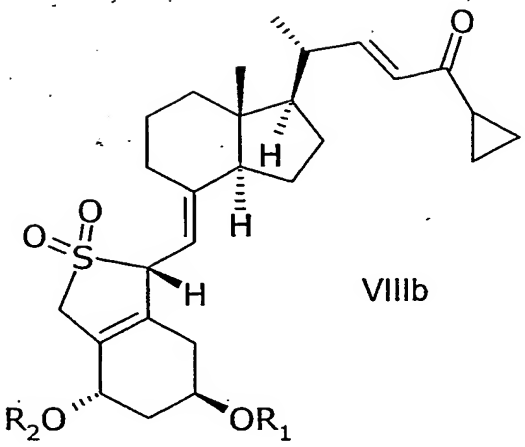
Va



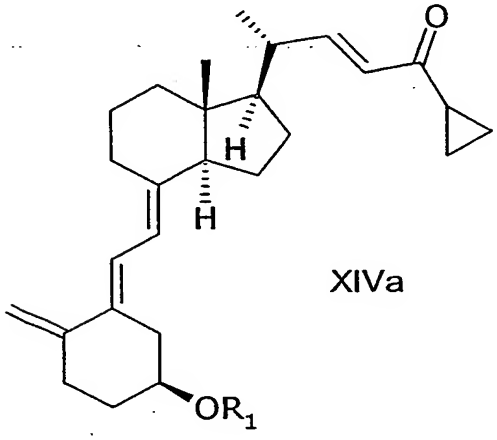
Vb



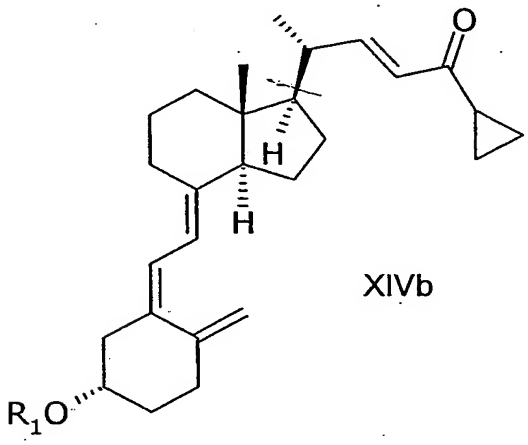
VIIIa



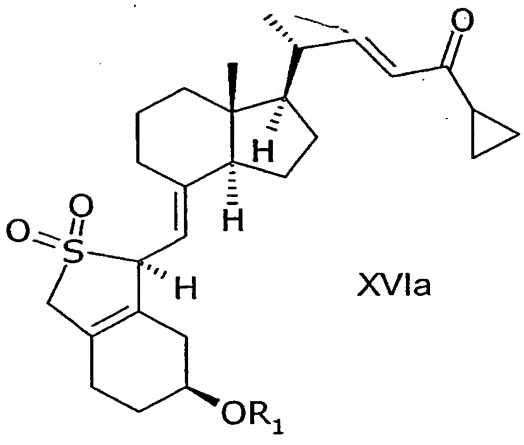
VIIIb



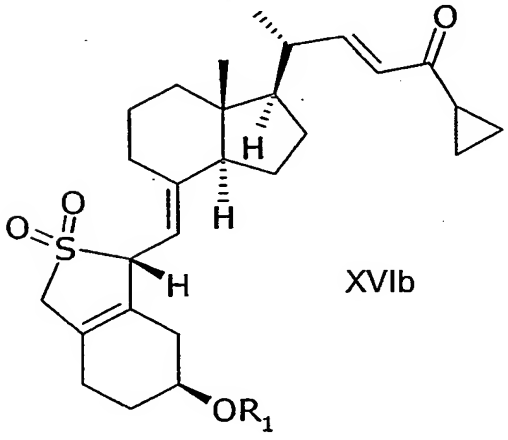
XIVa



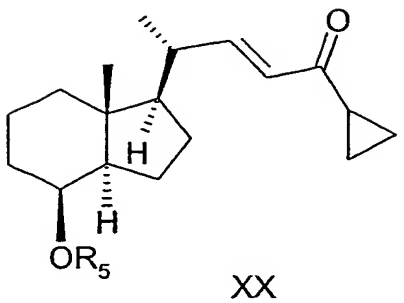
XIVb



XVIa



XVIb



XX

wherein R_1, R_2, and R_5 are as defined above.

This process, also called Wadsworth-Emmons, Wittig-Horner, or Horner-Emmons-Wadsworth reaction, has several advantages over the use of the phosphorane reagent IV: a) The reagent of general structure VII is more reactive than the corresponding phosphorane allowing the usage of mild reaction conditions such as low temperature, typically below 35°C. b) The phosphorus product of the reaction is a phosphate ester, and hence soluble in water, unlike triphenylphosphine oxide, which makes it easy to separate it from the enones Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, XVIb, or XX. c) The Wittig-Horner reaction is more trans-selective resulting in a better yield and in improved purity of the desired products Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, XVIb, or XX.

In a first aspect, this invention relates to a method of reacting a compound of general structure IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, XVb, or IXX as above with a phosphonate of general structure VII to give a compound of general structure Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, XVIb, or XX as above.

In another aspect, this invention relates to a compound of general structure Vb, wherein R_1 and R_2 are the same or different and each represent a hydroxy protecting group, or R_1 represents hydrogen and R_2 represents a hydroxy protecting group, or R_2 represents hydrogen and R_1 represents a hydroxy protecting group.

In yet another aspect, this invention relates to 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

In yet another aspect, this invention relates to a compound of general structure XIVa, wherein R_1 represents hydrogen or a hydroxy protecting group, with the proviso that R_1 cannot be *tert*-butyldimethylsilyl.

In yet another aspect, this invention relates to a compound of general structure XIVb, wherein R_1 represents hydrogen or a hydroxy protecting group.

In yet another aspect, this invention relates to a compound of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, provided that that the compound is not (2-cyclopropyl-2-oxoethyl)-phosphonic acid diethyl ester.

In yet another aspect, this invention relates to a compound of general structure IIIa, wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group, with the provisos that R_1 and R_2 cannot both be *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or triisopropylsilyl; with the further proviso that when R_2 is *tert*-butyldimethylsilyl, R_1 cannot be *tert*-butyldiphenylsilyl.

In yet another aspect, this invention relates to a compound of general structure IIIb, wherein R_1 represents a hydroxy protecting group, and R_2 represents hydrogen or a hydroxy protecting group; or R_1 represents a hydrogen or a hydroxy protecting group, and R_2 represents a hydroxy protecting group, except acetyl; with the proviso that R_1 and R_2 cannot both be *tert*-butyldimethylsilyl.

In yet another aspect, this invention relates to a compound of general structure VIa or VIb, wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group, with the proviso that R_1 and R_2 cannot both be *tert*-butyldimethylsilyl.

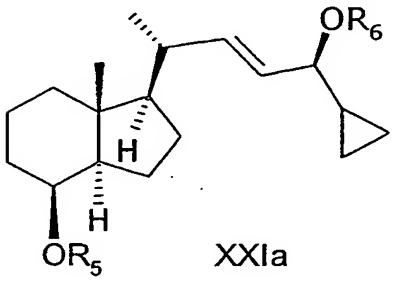
In yet another aspect, this invention relates to a compound of general structure XIIIa, wherein R_1 represents hydrogen or a hydroxy protecting group, except *tert*-butyldimethylsilyl.

In yet another aspect, this invention relates to a compound of general structure XIIIb, wherein R_1 represents a hydroxy protecting group, except *tert*-butyldimethylsilyl.

In yet another aspect, this invention relates to a compound of general structure XVa or XVb, wherein R_1 represents a hydroxy protecting group, except *tert*-butyldimethylsilyl, triisopropylsilyl, acetyl, or triethylsilyl.

In yet another aspect, this invention relates to a compound of general structure XX, wherein R_5 represents hydrogen or a hydroxy protecting group.

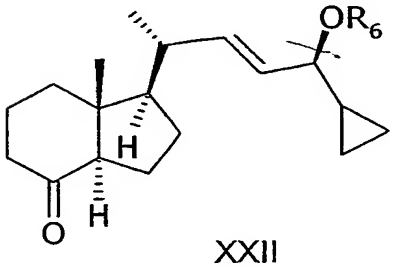
In yet another aspect, this invention relates to a compound of general structure XXIa,



XXIa

wherein R_5 and R_6 are the same or different and represent hydrogen or a hydroxy protecting group, with the provisos that when R_5 is hydrogen R_6 is not *tert*-butyldimethylsilyl, and when R_5 is benzoate, R_6 is not *tert*-butyldimethylsilyl or hydrogen.

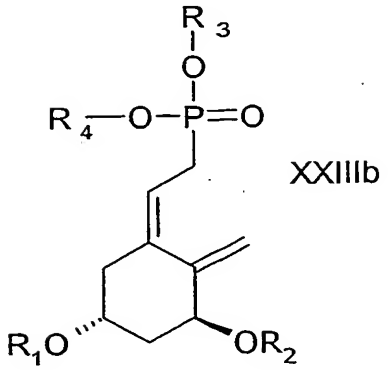
In yet another aspect, this invention relates to a compound of general structure XXII,



XXII

wherein R_6 represents hydrogen or a hydroxy protecting group, except *tert*-butyldimethylsilyl.

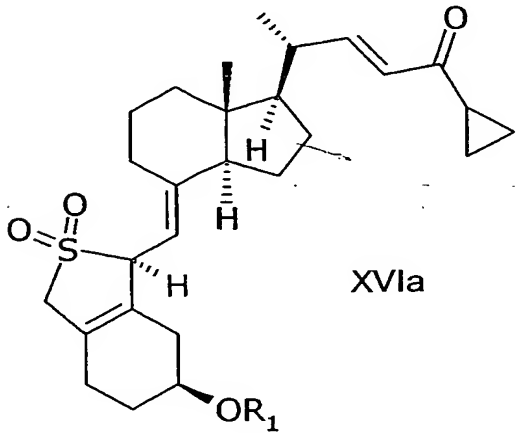
In yet another aspect, this invention relates to a compound of general structure XXIIIb,



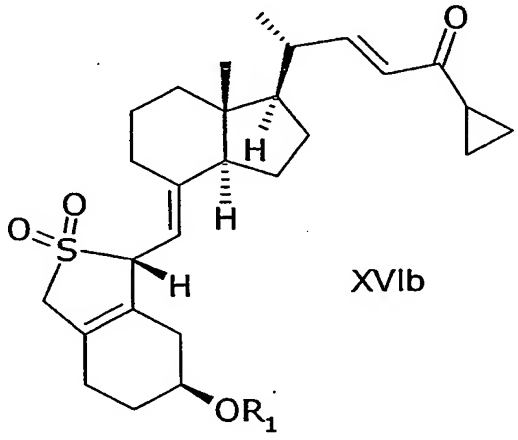
XXIIIb

wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group, and wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy.

In yet another aspect, this invention relates to a compound of general structure XVIa or XVIb,



XVIa



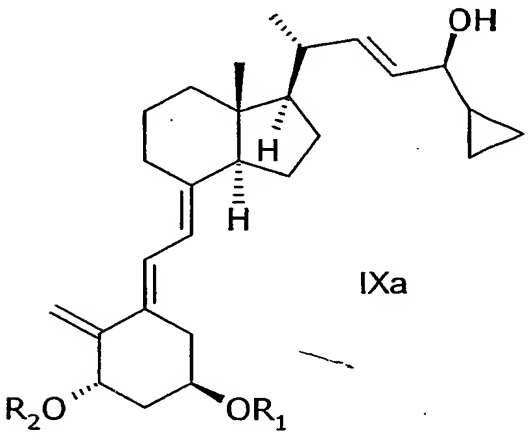
XVIb

wherein R_1 represents hydrogen or a hydroxy protecting group.

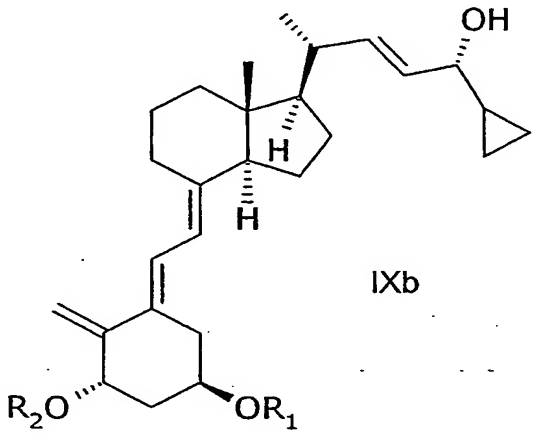
In a still further aspect, this invention relates to the use of a compound, such as a compound of general formula Vb, XIVa, XIVb, VII, IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, XVb, XX, XXIa, XXII, XXIIIB, or Va as defined above, as an intermediate in the manufacture of calcipotriol or calcipotriol monohydrate.

In a further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure IIIa,
wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group,
with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,
in the presence of a base, to give a compound of general structure Va, wherein R_1 and R_2 are as defined above;
(ii) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,

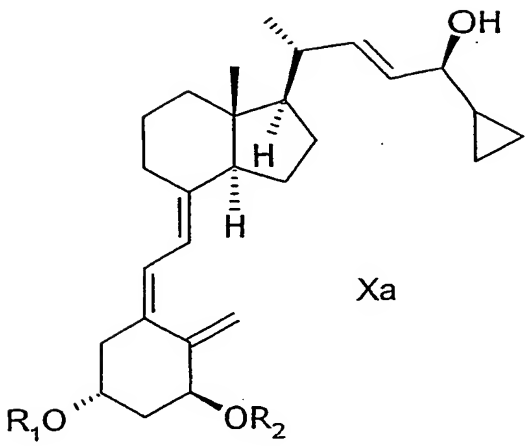


IXa



IXb

wherein R_1 and R_2 are as defined above;
(iii) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;
(iv) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(v) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(vi) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

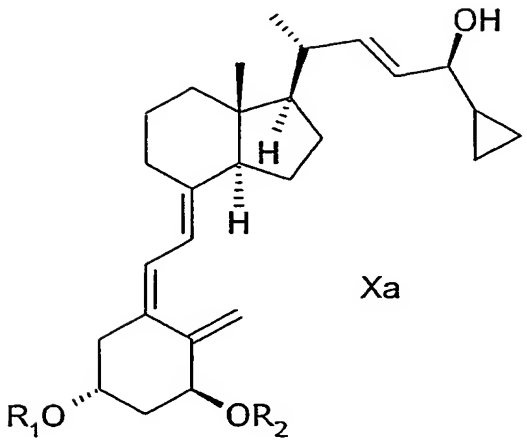
(i) reacting a compound of general structure IIIb,

wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group,

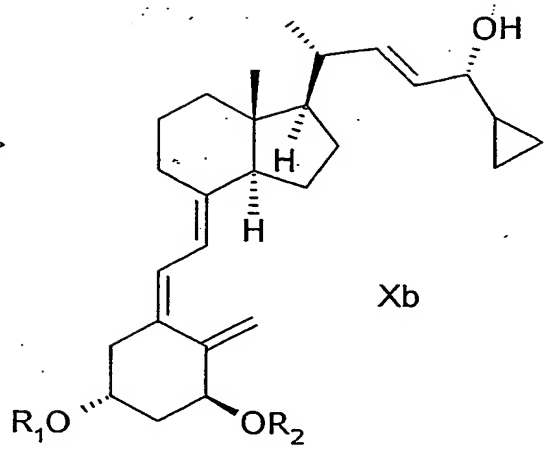
with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure Vb, wherein R_1 and R_2 are as defined above;

(ii) reducing the compound of general structure Vb with a suitable reducing agent to give a compound of general structure Xa or a mixture of compounds of general structure Xa and Xb,



Xa



Xb

wherein R_1 and R_2 are as defined above;

(iii) optionally separating the compound of general structure Xa from the mixture of compounds of general structure Xa and Xb;

(iv) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(v) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure VIa and/or VIb,

wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure VIIIa and/or VIIIb,

wherein R_1 and R_2 are as defined above;

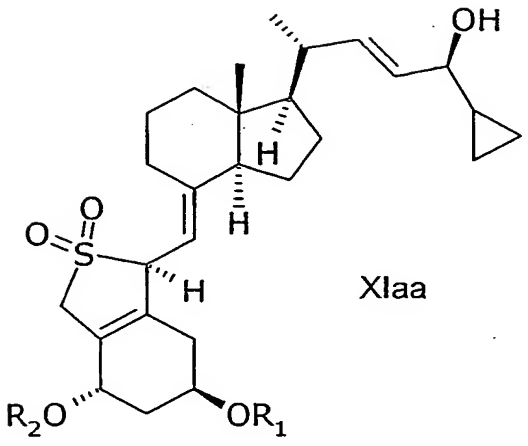
(ii) heating the compounds of general structure VIIIa and/or VIIIb above 60°C in the presence of a base to give a compound of general structure Va,

wherein R_1 and R_2 are as defined above;

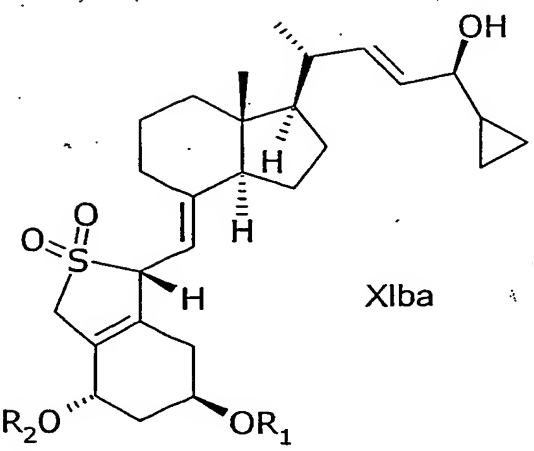
(iii) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,

wherein R_1 and R_2 are as defined above;
(iv) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;
(v) photoisomerising the compound of general structure IXa to the compound of general structure Xa,
wherein R_1 and R_2 are as defined above;
(vi) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and
(vii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

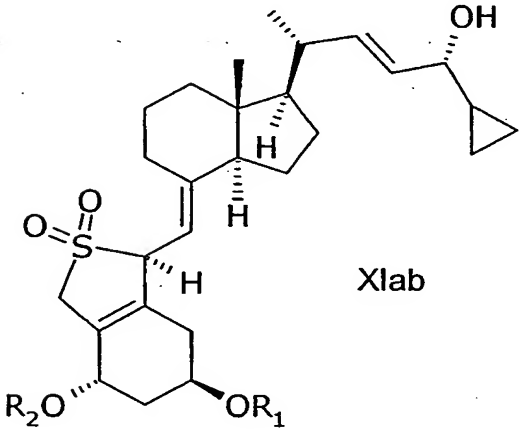
In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:
(i) reacting a compound of general structure VIa and/or VIb,
wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group,
with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,
in the presence of a base, to give a compound of general structure VIIIa and/or VIIIb,
wherein R_1 and R_2 are as defined above;
(ii) reducing the compounds of general structure VIIIa and/or VIIIb, with a suitable reducing agent in an inert solvent, to give compounds of general structure XIaa and/or XIba, or a mixture of compounds of general structure XIaa and/or XIba and XIab and/or XIbb,



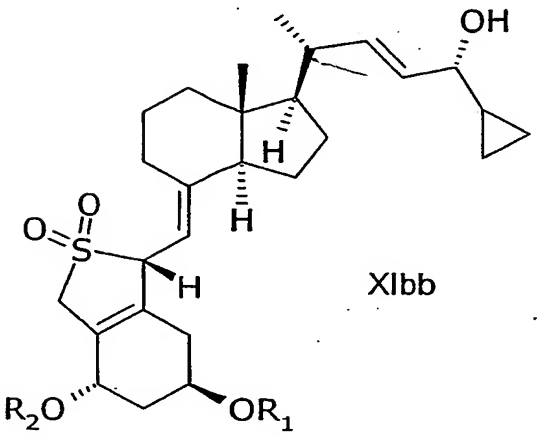
XIaa



XIba



XIab



XIbb

wherein R_1 and R_2 are as defined above;

(iii) optionally separating the compounds of general structure XIaa and/or XIba from the reaction mixture;

(iv) heating the compounds of general structure XIaa and/or XIba above 60°C in the presence of a base to give a compound of general structure IXa,

wherein R_1 and R_2 are as defined above;

(v) optionally separating the compound of general structure IXa from the reaction mixture;

(vi) photoisomerising the compound of general structure IXa to the compound of general structure Xa,

wherein R_1 and R_2 are as defined above;

(vii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(viii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate;

wherein steps (vi) and (vii) may be in reversed order.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure XIIIa,

wherein R_1 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XIVa, wherein R_1 is as defined above;

(ii) hydroxylating the compound of general structure XIVa with suitable hydroxylating agent to give a compound of general structure Va,

wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iii) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 are the same or different and represent a hydroxy protecting group;

(iv) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,

wherein R_1 and R_2 are as defined above;

(v) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vi) photoisomerising the compound of general structure IXa to a compound of general structure Xa,

wherein R_1 and R_2 are as defined above;

(vii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(viii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure XIIIb,

wherein R_1 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XIVb, wherein R_1 is as defined above;

(ii) photoisomerising the compound of general structure XIVb to a compound of general structure XIVa,

wherein R_1 is as defined above;

(iii) hydroxylating the compound of general structure XIVa with suitable hydroxylating agent to give a compound of general structure Va,

wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iv) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 are the same or different and represent a hydroxy protecting group;

(v) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,

wherein R_1 and R_2 are as defined above;

(vi) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vii) photoisomerising the compound of general structure IXa to the compound of general structure Xa,

wherein R_1 and R_2 are as defined above;

(viii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(ix) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure XVa and/or XVb,

wherein R_1 represents a hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XVIa and/or XVIb, wherein R_1 is as defined above;

(ii) heating the compounds of general structure XVIa and/or XVIb above 60°C in the presence of a base to give a compound of general structure XIVa,

wherein R_1 is as defined above;

(iii) hydroxylating the compound of general structure XIVa with suitable hydroxylating agent to give a compound of general structure Va,

wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iv) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 are the same or different and represent a hydroxy protecting group;

(v) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,

wherein R_1 and R_2 are as defined above;

(vi) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vii) photoisomerising the compound of general structure IXa to the compound of general structure Xa,

wherein R_1 and R_2 are as defined above;

(viii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(ix) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure IXX,

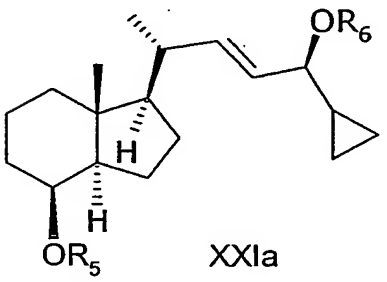
wherein R_5 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII,

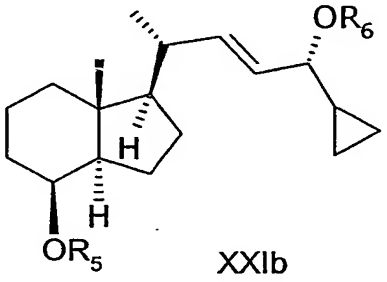
wherein R_3 and R_4 are the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base,

to give a compound of general structure XX, wherein R_5 is as defined above;

(ii) reducing the compound of general structure XX with a suitable reducing agent to give a compound of general structure XXIa or a mixture of compounds of general structure XXIa and XXIb, wherein R_5 is as defined above and R_6 is hydrogen;



XXIa



XXIb

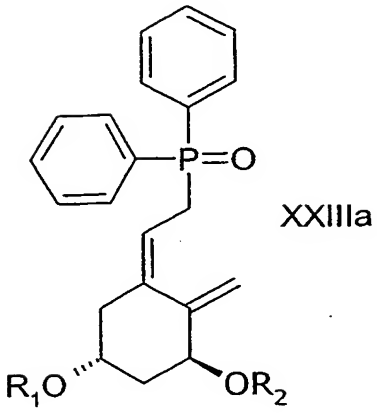
(iii) optionally separating the compound of general structure XXIa from the mixture of compounds of general structure XXIa and XXIb;

(iv) protecting the allylic hydroxy group of the compound of general structure XXIa with a suitable hydroxy protecting reagent to give a compound of general structure XXIa, wherein R_6 is a hydroxy protecting group and R_5 is as defined above;

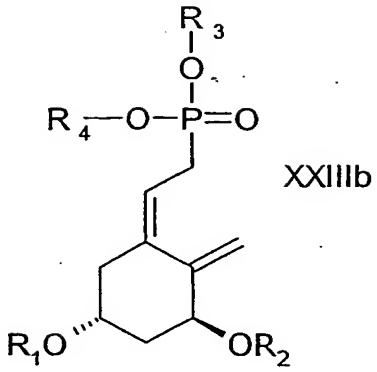
(v) when R_5 is not hydrogen, removing the hydroxy protecting group R_5 of the compound of general structure XXIa to give a compound of general structure XXIa, wherein R_5 is hydrogen;

(vi) oxidising the hydroxy group of the compound of general structure XXIa with a suitable oxidising agent to give a compound of general structure XXII, wherein R_6 is as defined above;

(vii) coupling of the compound of general structure XXII with a Wittig reagent XXIIIa or a Wittig Horner reagent XXIIIb, wherein R_1 and R_2 represent a hydrogen or a hydroxy protecting group, and wherein R_3 and R_4 are as defined above;

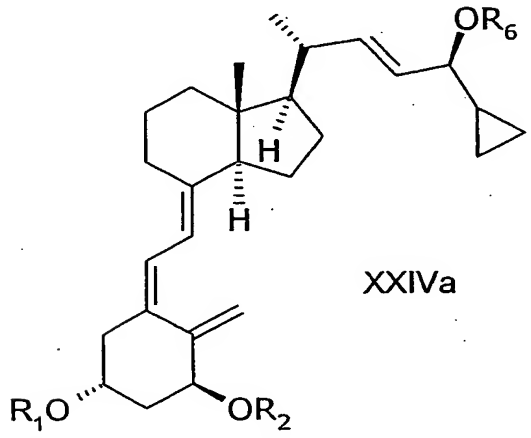


XXIIIa



XXIIIb

in the presence of a base to give a compound of general structure XXIVa,



XXIVa

wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group, and wherein R_6 is as defined above;

(viii) when R_6 is not hydrogen, removing the hydroxy protecting group R_6 of the compound of general structure XXIVa;

(ix) optionally separating the compound of general structure XXIVa;

(x) when R_1 and R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and R_2 of the compound of general structure XXIVa to generate calcipotriol;

and

(xi) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

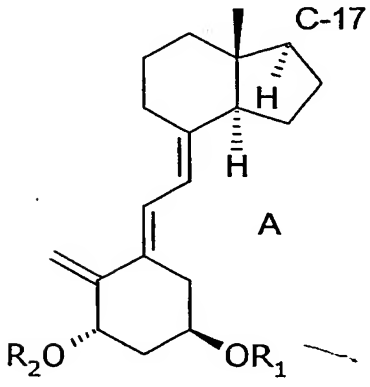
DETAILED DESRIPTION OF THE INVENTION

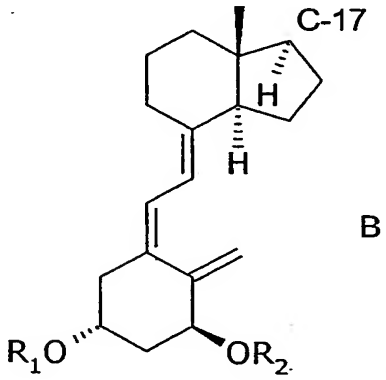
Definitions

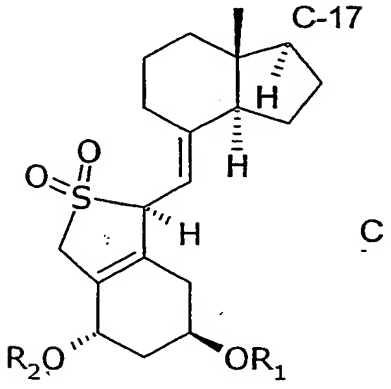
As used herein, "vitamin D-analogue" means any derivative of vitamin D_2 or D_3, such as 1α,25-dihydroxyvitamin D_2 or 1α,25-dihydroxyvitamin D_3, including derivatives wherein

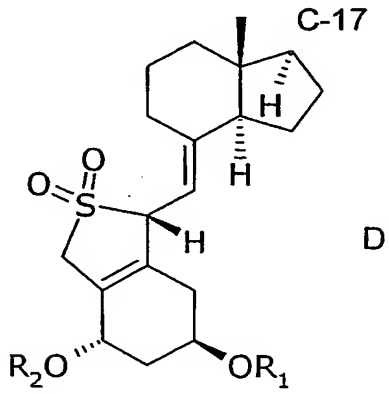
one or more of the A, C, or D ring are modified or/and where the side chain attached to C-17 is different from natural vitamin D_2 or D_3. Examples of vitamin D-analogues can for example be found in ["Vitamin D", D. Feldman, Ed., Academic Press, San Diego, USA, 1997] and [G.-D. Zhu et al., Chem. Rev. 1995, 95, 1877-1952] and references cited therein, and include hydroxy protected or unprotected calcipotriol, and isomers and derivatives of calcipotriol.

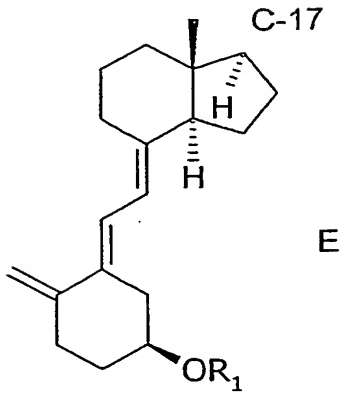
As used herein, "vitamin D-analogue fragment" means a C-17 radical of a vitamin D-analogue as defined above without the side chain usually attached at C-17. Examples of vitamin D-analogue fragments are represented by structures A, B, C, D, E, F, G, H; wherein the C-17 analogous positions in the sense of the present invention are indicated below; and wherein R_1 and R_2 are the same or different and represent hydrogen or a hydroxy protecting group.



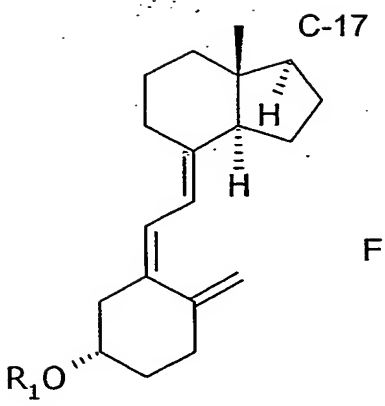




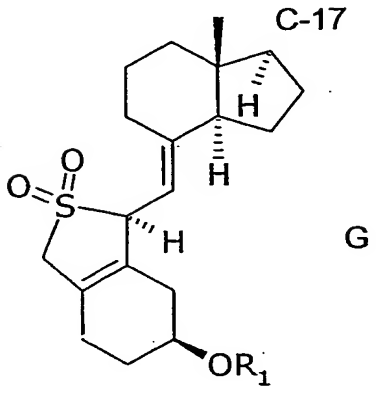




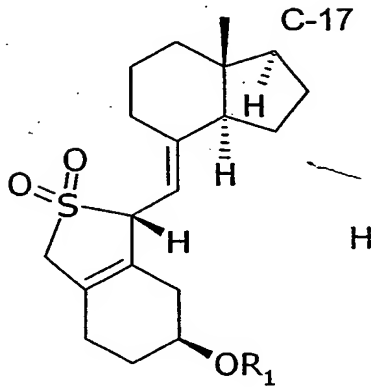
E



F

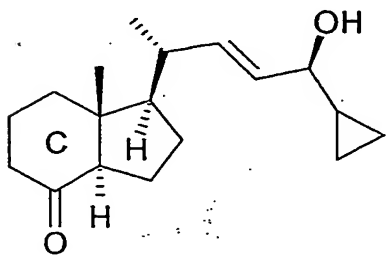


G

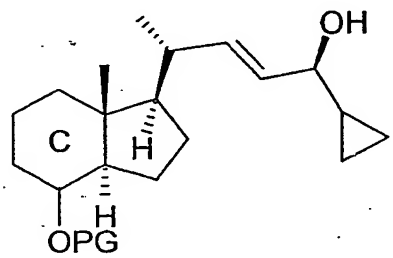


H

As used herein, "a precursor for the synthesis of a vitamin D-analogue" means any molecule useful in the synthesis of a vitamin D derivative as defined above, such as a starting material or intermediate, wherein part of the precursor molecule becomes incorporated into the final vitamin D-analogue. Examples include, but are not limited to steroid ring systems, such as ergosterol, cholesterol, or 7-dehydrocholesterol, or derivatives of the CD-rings of steroids, such as Grundmann's ketone or derivatives of Grundmann's ketone. Examples of precursors for the synthesis of a vitamin D-analogue can for example be found in [G.-D. Zhu et al., Chem. Rev. 1995, 95, 1877-1952] and references cited therein. Examples of specific derivatives of CD-rings of steroids, which are in particular useful are the ring structures M and N illustrated below, wherein PG is hydrogen or a hydrogen protecting group as defined below.



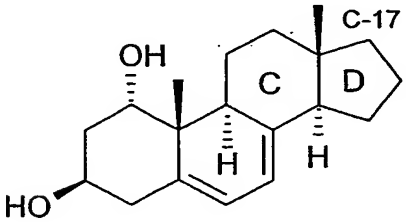
M



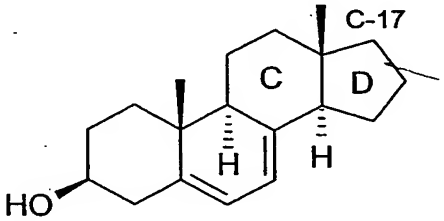
N

A C-17 analogous position of such a precursor is intended to mean the carbon atom of said precursor, which will correspond to the C-17 carbon atom in the final vitamin D-analogue or calcipotriol.

As used herein, "a fragment of a precursor for the synthesis of a vitamin D-analogue" means a radical of a precursor for the synthesis of a vitamin D-analogue as defined above. For example a fragment of a precursor for the synthesis of a vitamin D-analogue may be a steroid ring system fragment, which may be represented by structure Q or R, wherein the C-17 analogous positions in the sense of the present invention are indicated below.

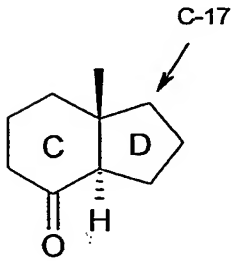


Q

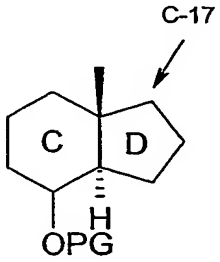


R

Other examples of fragments of a precursor for the synthesis of a vitamin D-analogue are fragments of derivatives of the CD-rings of steroids, which may for example be represented by structure O or P, wherein the C-17 analogous positions in the sense of the present invention are indicated and wherein PG is as defined above.



O



P

As used herein a "hydroxy protecting group" is any group which forms a derivative that is stable to the projected reactions wherein said hydroxy protecting group can be selectively removed by reagents that do not attack the regenerated hydroxy group. Said derivative can be obtained by selective reaction of a hydroxy protecting agent with a hydroxy group. Silyl derivatives, e.g. trialkylsilyl, such as *tert*-butyldimethylsilyl, trimethylsilyl, triethylsilyl, diphenylmethylsilyl, triisopropylsilyl, *tert*-butyldiphenylsilyl,

forming silyl ethers are examples of hydroxy protecting groups. Silyl chlorides such as *tert*-butyldimethylsilyl chloride (TBSCl), trimethylsilylchloride, triethylsilylchloride, diphenylmethylsilylchloride, triisopropylsilylchloride, and *tert*-butyldiphenylsilylchloride are examples of hydroxy protecting agents. Silyl chlorides are for example reacted with the hydroxy group(s) in the presence of a base, such as imidazole. Hydrogen fluoride, such as aqueous HF in acetonitrile, or tetra n-butylammonium fluoride are examples of reagents which can remove silyl groups. Other hydroxy protecting groups include ethers, such as tetrahydropyranyl (THP) ether, benzyl ether, *tert*-butyl ether, including alkoxyalkyl ethers (acetals), such as methoxymethyl (MOM) ether, or esters, such as chloroacetate ester, trimethylacetate, acetate or benzoate ester. Non-limiting examples of hydroxy protecting groups and methods of protection and removal, all included in the scope of this application, can for example be found in "Protective Groups in Organic Synthesis", 3rd ed., T. W. Greene & P. G. M. Wuts eds., John Wiley 1999 and in "Protecting Groups", 1st ed., P.J. Kocienski, G. Thieme 2000, Jarowicki, K., Kocienski, P., *J. Chem. Soc., Perkin Trans.* 1, 2000, 2495-2527, all of which are hereby incorporated by reference.

As used herein, "alkyl" is intended to mean a linear or branched alkyl group, which may be cyclic or acyclic, having one to twenty carbon atoms, such as 1-12, such as 1-7, such as 1-4 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl, *tert.*-butyl, pentyl, isopentyl, hexyl, isohexyl, and the *tert*-butyldimethyl group.

The term "halogen" is intended to indicate a substituent from the 7th main group of the periodic table, preferably fluoro, chloro and bromo.

The term "alkenyl" is intended to indicate a mono-, di-, tri-, tetra- or pentaunsaturated hydrocarbon radical comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as 2-4 carbon atoms, e.g. ethenyl, propenyl, butenyl, pentenyl or hexenyl.

The term "alkynyl" is intended to indicate an hydrocarbon radical comprising 1-5 triple C-C bonds and 2-20 carbon atoms, the alkane chain typically comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as 2-4 carbon atoms, e.g. ethynyl, propynyl, butynyl, pentynyl or hexynyl.

The term "haloalkyl" is intended to indicate an alkyl group as defined above substituted with one or more halogen atoms as defined above.

The term "hydroxyalkyl" is intended to indicate an alkyl group as defined above substituted with one or more hydroxy groups.

The term "alkoxy" is intended to indicate a radical of the formula –OR', wherein R' is alkyl as indicated above, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, etc.

The term "alkoxycarbonyl" is intended to indicate a radical of the formula –C(O)-O-R', wherein R' is alkyl as indicated above, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, etc.

The term "alkylcarbonyloxy" is intended to indicate a radical of the formula –O-C(O)-R', wherein R' is alkyl as indicated above.

The term "cycloalkyl" is intended to indicate a saturated cycloalkane radical comprising 3-20 carbon atoms, preferably 3-10 carbon atoms, in particular 3-8 carbon atoms, such as 3-6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "cycloalkenyl" is intended to indicate mono-, di- tri- or tetraunsaturated non-aromatic cyclic hydrocarbon radicals, comprising 3-20 carbon atoms, typically comprising 3-10 carbon atoms, such as 3-6 carbon atoms, e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

The term "aryl" is intended to indicate a radical of aromatic carbocyclic rings comprising 6-20 carbon atoms, such as 6-14 carbon atoms, preferably 6-10 carbon atoms, in particular 5- or 6-membered rings, optionally fused carbocyclic rings with at least one aromatic ring, such as phenyl, naphthyl, indenyl and indanyl.

The term "aralkyl" is intended to indicate an alkyl group as defined above substituted with one or more aryl radicals as defined above.

The term "aralkenyl" is intended to indicate an alkenyl group as defined above substituted with one or more aryl radicals as defined above.

The term "aralkynyl" is intended to indicate an alkynyl group as defined above substituted with one or more aryl radicals as defined above.

As used herein "suitable reducing agent" is intended to mean any agent capable of reducing, preferably enantioselectively or diastereoselectively reducing, the C-24 keto group of a compound of general structure XX, Va, Vb, VIIIa, or VIIIb to give preferably a compound of general structure XXIa (R_6=hydrogen), IXa, Xa, XIaa, or XIba respectively. Examples of reducing agents include, but are not limited to borane reducing agents, metallic hydrides, such as lithium aluminium hydride, sodium borohydride, or AlH_3, optionally in the presence of lanthanide salts (e.g. $LaCl_3$, $CeBr_3$, $CeCl_3$), or $NaBH_3(OAc)$, $Zn(BH_4)_2$, and Et_3SiH. Borane reducing agents include borane, borohydrides, and borane complexes with amines or ethers. Non-limiting examples of borane reducing agents e.g. include *N,N*-diethylaniline-borane, borane-tetrahydrofuran, 9-borabicyclononane (9-BBN), or borane dimethylsulfide. Other reducing agents include, but are not limited to, hydrogen in the presence of a catalyst, such as platinum or ruthenium, sodium in ethanol, isopropyl alcohol and aluminium isopropoxide, and zinc powder in water or alcohol.

When reducing the C-24 keto group of a compound of general structure XX, XVIa, XVIb, VIIIa, or VIIIb, the term "suitable reducing agent" includes chiral reducing agents or chiral ligand-reducing agent complexes, such as the complex of $LiAlH_4$ and 2,2'-dihydroxy-1,1'binaphthyl . Other examples are hydrogen in the presence of binaphthyl derivatives, such as 2,2'-dihydroxy-1,1'binaphthyl derivatives, e.g. (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-ruthenium acetate.

Chiral reducing agents or chiral ligand-reducing agents include reducing agents where a chiral auxiliary is reacted with the reducing agent prior to the reduction *in situ* to form a chiral reducing agent or the where the chiral auxiliary may for example serve as a chiral ligand in a complex with the reducing agent, i.e. for example to give a chiral reducing agent. The present invention includes the use of such chiral reducing agents or chiral ligand-reducing agent complexes, which were prepared and isolated separately before being used for the reduction.

For example, the chiral auxiliary may react with a borane reducing agent prior to the reduction *in situ* to form a chiral borane reducing agent or the chiral auxiliary may serve as a chiral ligand in a borane complex. Examples of such chiral borane reducing agents are chiral oxaborolidines or oxazaborolidines, such as chiral oxazaborolidine reagents derived from (1R,2S)-*cis*-1-amino-2-indanol, (1S,2R)-*cis*-1-amino-2-indanol, (S)-prolinol, (R)-prolinol or B-(3-pinanyl)-9-borabicyclo[3.3.2]nonane (alpine-borane), or e.g. 5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, (S)-2-methyl-CBS-oxazaborolidine, (R)-2-methyl-CBS-oxazaborolidine. The present invention therefore includes the use of such chiral reducing agents, such as chiral borane reducing agents,

or chiral ligand-reducing agent complexes, such as chiral ligand-borane complexes, which were prepared and isolated before being used for the reduction.
Another example of a chiral ligand in a complex with the reducing agent is the complex of $LiAlH_4$ and 2,2'-dihydroxy-1,1'binaphthyl.

The reduction of a compound of general structure XX, XVIa, XVIb, VIIIa, or VIIIb may be carried out in the presence of a chiral auxiliary, such as in an inert solvent. Non-limiting examples of chiral auxiliaries include chiral 1,2-amino-alcohols, such as chiral *cis*-1-amino-2-indanol derivatives, such as (*1S,2R*)-(-)-*cis*-1-amino-2-indanol, or *cis*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol, such as (*1S,2R*)-*cis*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol. Other examples are binaphthyl derivatives, such as (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-ruthenium acetate 2,2'-dihydroxy-1,1'binaphthyl derivatives. Further examples include but are not limited to (R)-(+)-α,α-diphenyl-2-pyrrolidinmethanol, (R)-(+)-2-amino-4-methyl-1,1-diphenyl-1-pentanol, (R)-(-)-2-amino-3-methyl-1,1-diphenyl-1-butanol, (R)-(+)-2-amino-1,1,3-triphenyl-1-propanol, and (1R,2S)-(-)-2-amino-1,2-diphenyl ethanol.

As used herein, "separating a compound" includes the purification and/or isolation of a compound, e.g. to at least 90% purity, such as to at least 95% purity, such as 97% purity, 98% purity, or 99% purity. The term "separating a compound" also includes the meaning of enhancing the concentration of the compound in a mixture of such compounds, optionally comprising solvents, such that the mixture is further enriched with a desired or preferred compound or isomer, such as an epimer, after said separation. Most preferably R_1 and/or R_2 represent alkylsilyl, such as *tert*-butyldimethylsilyl, and most preferably R_1 and R_2 are the same, and R_6 is hydrogen when compounds of the present invention are separated by chromatography.

As used herein, "inert solvent" means any organic solvent compatible with said suitable reducing agent under the reaction conditions employed, or mixtures of such solvents. The choice of such solvent will depend on the specific reducing agent used. Non-limiting examples of inert solvents include hydrocarbons, such as toluene, and ethers, such as *tert*-butyl methyl ether or tetrahydrofuran.

Preferred embodiments

In another aspect, this invention relates to 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene obtained by a process comprising the method of reacting a compound of general structure IIIa with a phosphonate of general structure VII.

In a further aspect, this invention relates to 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene obtained by a process comprising the method of reacting a compound of general structure IIIb with a phosphonate of general structure VII.

In a still further aspect, this invention relates to the SO_2 adducts of 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene obtained by a process comprising the method of reacting a compound of general structure VIa or VIb with a phosphonate of general structure VII.

In a currently preferred embodiment of the present invention R_1 and/or R_2 represent alkylsilyl, such as *tert*-butyldimethylsilyl, most preferably R_1 and R_2 are the same.
In another embodiment of the present invention R_1 and/or R_2 represent hydrogen, most preferably R_1 and R_2 are the same.

In a currently preferred embodiment of the present invention R_3 and/or R_4 represent alkyl, such as (C_1-C_6)alkyl, such as methyl, ethyl, or 1-propyl, most preferably R_3 and R_4 are the same.

In one embodiment of the present invention the hydroxy protecting group R_5 is alkylsilyl, such as triethylsilyl, and the hydroxy protecting group R_6 is alkylsilyl, such as *tert*-butyldimethylsilyl.

Compounds and intermediates of the present invention may comprise asymmetrically substituted (chiral) carbon atoms and carbon-carbon double bonds which may give rise to the existence of isomeric forms, e.g. enantiomers, diastereomers and geometric isomers. Epimers are known as diastereomers that have opposite configuration (R or S) at only one of multiple tetrahedral stereogenic centres in molecules having multiple stereogenic centres, such as the vitamin D analogues to which the present invention is directed. Designation of, for example, C-24 as the epimeric centre of a pair of enantiomers therefore implies that the configuration at the other stereogenic centres of the pair are identical. The present invention relates to all isomeric forms, such as epimers, either in pure form or as mixtures thereof. Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of procedures known in the art, such as by chromatography or crystallisation, or by stereoselective synthesis.

The indication of a specific conformation or configuration either in the formulas or the names of compounds or intermediates of the present invention shall indicate that this

specific conformation or configuration is a preferred embodiment of the invention. The indication of a specific conformation or configuration either in the formulas or the names of compounds or intermediates of the present invention shall include any other isomer than specifically indicated, either in pure form or as mixtures thereof, as a further embodiment of the present invention.

Methods of preparation

Compounds of general structure IIIa can for example be synthesised according to methods disclosed for example by M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 or in WO 87/00834. For example compound IIIa, wherein both R_1 and R_2 are *tert*-butyldimethylsilyl which preparation is described in these references can be deprotected with aqueous hydrofluoric acid in acetonitrile or with tetrabutylammonium fluoride to give a mixture of compounds wherein R_1 or R_2 are hydrogen, or to give a compound wherein R_1 and R_2 are hydrogen. This mixture of compounds can for example be separated by chromatography or crystallised as generally described herein. By reaction of said compounds of general structure IIIa, wherein R_1 and/or R_2 are hydrogen with a suitable protecting agent, new groups R_1 and/or R_2 can be introduced. Depending on the stoichiometry of the protecting agent used and the reaction conditions, mixtures of unprotected, monoprotected, and deprotected compounds can be obtained. Any intermediate of a mixture wherein one of R_1 or R_2 is hydrogen can then be isolated by chromatography and reacted with suitable protecting agent different from the first one used, to give compounds of general structure IIIa, wherein R_1 is different from R_2.

Compounds of general structure IIIb can be obtained from compounds of general structure IIIa by photo isomerisation, such as with UV-light in the presence of a triplet sensitizer, such as anthracene or 9-acetylanthracene. Such processes are well known to a person skilled in the art of vitamin D-derivatives and are for example described by M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 or in WO 87/00834 which are herby incorporated by reference.

Compounds of general structure VIa and/or VIb can be obtained from compounds of general structure IIIa or IIIb by treatment of a compound of general structure IIIa or IIIb with sulphur dioxide. The sulphur dioxide used can be liquid, gaseous or being dissolved in a suitable solvent. Suitable solvents for this Diels-Alder type reaction are all solvents, which are compatible with the reaction conditions, such as alkanes, such as hexane or heptane, hydrocarbons, such as xylenes, toluene, ethers, such as diethyl ether or methyl-*tert*-butyl ether (MTBE), acetates, such as ethyl acetate or 2-propyl

acetate, halogenated solvents such as dichloromethane, or mixtures of said solvents, such as a mixture of a water immiscible solvent and water, e.g. toluene and water. The reaction can also be carried out in neat sulphur dioxide without a solvent. A suitable reaction temperature of the process is -50°C to 60 °C, such as -30°C to 50°C, such as -15°C to 40°C, such as -5°C to 30°C, such as 0°C to 35°C, such as 5°C to 30°C most such as 10°C to 25°C, such as 15°C to 20°C. Preferably the sulphur dioxide is used in excess (mol/mol), such as 5-100 molar excess, such as 7-30 molar excess, such as 10-15 molar excess. Any excess of unreacted sulphur dioxide can be removed from the reaction mixture by e.g. washing with aqueous base, such as aqueous sodium hydroxide or by distilling the sulphur dioxide off, optionally together with a solvent, optionally under reduced pressure. Reacting compounds of general structure IIIa with sulphur dioxide usually leads to mixtures of the two epimers VIa and VIb. The molar ratio VIa/VIb of the mixture of the epimers obtained in the Diels-Alder reaction will depend on the groups R_1 and R_2 and the reaction conditions used.

Compounds of general structure XVa and XVb can for example be synthesised as previously described in EP 0078704 for R_1 = *tert*-butyldimethylsilyloxy (Example 11 (c). Compounds XVa and XVb, wherein R_1 is *tert*-butyldimethylsilyl can for example be deprotected with a suitable deprotecting reagent, such as aqueous hydrofluoric acid in acetonitrile or with tetrabutylammonium fluoride to give compounds, wherein R_1 is hydrogen, which then can be reacted with a suitable protecting agent, to give compounds of general structure XVa and XVb with a group R_1 different from the starting compound. Furthermore compounds of general structure XVa and XVb can be synthesised by ozonolysis of compounds 6a, 6b, 7a, or 7b disclosed in Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987.

Compounds of general structure XIIIa can for example be synthesised starting from the sulphur dioxide adducts XVa and XVb by base assisted retro Diels-Alder reaction, such as described below. Different groups R_1 may be introduced, before or after the retro Diels-Alder reaction, by methods well known to a person skilled in the art of organic chemistry and as for example described above for compounds of general structure IIIa.

Compounds of general structure XIIIb can be obtained from compounds of general structure XIIIa, and vice versa, by photo isomerisation as described above.

The C,D-ring building blocks of general structure IXX can for example be prepared from vitamin D_2 (ergocalciferol) by methods disclosed in Eur. J. Org. Chem, 2003, 3889-3895; J. Med. Chem. 2000, 43, 3581-3586; J. Med. Chem. 1995, 38, 4529-4537, Chemical Reviews, 1995, Vol. 95, No.6, and J. Org. Chem. 1992, 57, 3173-3178. Different groups R_5 can be introduced by using standard protection group chemistry such as described herein.

The sulphur dioxide adducts of the present invention are preferably converted to the unprotected triene derivatives in the presence of a base in a retro Diels-Alder reaction. The reaction may be carried out in all solvents, which are compatible with the reaction conditions, such as alkanes, such as hexane or heptane, hydrocarbons, such as xylenes, toluene, ethers, such as diethyl ether or methyl-*tert*-butyl ether (MTBE), acetates, such as ethyl acetate or 2-propyl acetate, halogenated solvents such as dichloromethane, water or mixtures of said solvents. Methods of this retro Diels Alder type reaction are well known to a person skilled in the art of vitamin D synthesis (see e.g. M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 or in WO 87/00834). Preferred solvents are toluene, *tert*-butyl methyl ether, water, or mixtures thereof. Suitable bases to be used in the retro Diels-Alder reaction include, but are not limited to $NaHCO_3$, $KHCO_3$, Na_2CO_3, or K_2CO_3. In a preferred embodiment of the present invention, the base is aqueous $NaHCO_3$ and/or the retro Diels-Alder reaction is run above 60°C, such as between 60°C and 120 °C, most preferably above 70°C, such as between 74°C and 79 °C, typically for about one-two hours.

Compounds of general structure VIa and/or VIb can be further obtained by ozonolysis of the SO_2 adducts of 1(S),3(R)-bis(tert-butyldimethylsilyloxy)-9,10-seco-ergosta-5,7(E),10(19),22(E)-tetraene as for example described in Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987, optionally followed by deprotection and protection of the hydroxy groups as described above for compounds of general structure IIIa and/or IIIb.

The synthetic methods used in the present invention are well known to a person skilled in the art of vitamin D synthesis or organic chmistry. Suitable reaction conditions can e.g. be found in Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987, in WO 87/00834, in WO 94/15912, in US 69,553,962, and in Chemical Reviews, 1995, Vol. 95, No.6; and the references cited therein, all of which hereby are incorporated by reference.

The reduction of the compounds of general structure VIIIa and/or VIIIb, or XVIa and/or XVIb respectively, or XX is preferably carried out by reacting with a chiral borane

reducing agent, such as a chiral oxaborolidines or oxazaborolidines, such as chiral oxazaborolidine reagents derived from *N,N*-diethylaniline-borane and (1S,2R)-*cis*-1-amino-2-indanol, (1R,2S)-*cis*-1-amino-2-indanol, (1S,2R)-*cis*-1-amino-2-indanol, (S)-prolinol, (R)-prolinol or B-(3-pinanyl)-9-borabicyclo[3.3.2]nonane (alpine-borane), or e.g. 5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, (S)-2-methyl-CBS-oxazaborolidine, (R)-2-methyl-CBS-oxazaborolidine. These reduction methods and methods for the preparation of the compounds of general structure VIIIa and/or VIIIb have been described in detail in US Appl. No. 60/553,962. The molar ratio of chiral auxiliary/reducing agent is preferably in the range of 2.3-2.7. The reduction reaction is usually carried out in a temperature interval between 5°C to 35°C, preferably 10°C to 30°C, preferably 15°C to 25°C, most preferably 15°C to 20°C. The reducing agent is preferably used in an equimolar amount or in molar excess to a compound of general structure VIIIa and/or VIIIb, or XVIa and/or XVIb respectively, or XX, such as in 2.5-3.0 molar excess.

The process results in the enantioselective/diastereoselective reduction of the prochiral ketone of general structure VIIIa and/or VIIIb, or XVIa and/or XVIb respectively, or XX, such that the C-24 epimers XIa and/or XIb, or XVIa and/or XVIb respectively, or XXIa (R_6=hydrogen) are formed in preference. Such borane-catalysed reactions were for example reviewed by Deloux and Srebnik [Chem. Rev. 93, 763, 1993]. Examples of efficient catalysts based on chiral modified borane can for example be found in [A. Hirao, J. Chem. Soc. Chem. Commun. 315, 1981; E.J. Corey, J. Am. Chem. Soc. 109, 7925, 1987]. Examples of the synthesis and/or use of e.g. 1,2- and 1,3-amino alcohols in stereoselective reduction with borane can e.g. be found in [E. Didier *et al.*; Tetrahedron 47, 4941-4958, 1991; C.H. Senanayake *et al.*, Tetrahedron Letters, 36(42), 7615-18, 1995, EP 0698028, EP 0640089, EP 0305180, WO 93/23408, WO 94/26751]. The synthesis and/or use of chiral *cis*-1-amino-2-indanol derivatives in borane reductions can e.g. be found in [C.H. Senanayake, Aldrichimica Acta, 31 (1), 1-15, 1998; A.K. Ghosh *et. al.*, Synthesis, 937-961, 1998; Y. Hong *et. al.*, Tetrahedron Letters, 35(36), 6631-34, 1994; B. Di Simone, Tetrahedron Asymmetry, 6(1) 301-06, 1995; Y. Hong *et al.*, Tetrahedron Letters, 36(36), 6631-34, 1994; R. Hett *et al.*, Org. Process Res. & Dev., 2, 96-99, 1998; or EP 0763005], and references cited therein.

The method for producing calcipotriol as described herein may be modified with regard to the order of the reaction steps, by omitting one or more reaction steps, or by introducing additional purification or reaction steps at any stage of the reaction sequence. The present invention includes all such modifications. A person skilled in the

art of vitamin D chemistry or organic chemistry will know where such modifications can be made.

The method for producing calcipotriol as described herein includes further all variants, where the hydroxy protecting groups R_1 and/or R_2 for compounds or intermediates, where R_1 and/or R_2 are not hydrogen, are removed at any stage of the reaction sequence. Compounds or intermediates, where R_1 and/or R_2 are hydrogen may be protected with protecting agents at any stage of the reaction sequence, including protecting agents which yield other protecting groups than those removed earlier in the reaction sequence.

The reduction of a compounds of general formula XIVa, XIVb, XVIa, XVIb, XX, Va, Vb, VIIIa, and/or VIIIb with a suitable reducing agent in an inert solvent will, depending on the reducing agent and the reaction conditions used, give a mixture of the C-24 epimers of the corresponding alcohols formed, such as the compounds of general structures IXa and IXb, or such as the compounds of general structure Xa and Xb, or such as the compounds of general structure XIaa and XIab or XIba and XIbb, or such as XXIa and XXIb. Depending of the composition of the mixture, the desired epimers XXIa, IXa, Xa, XIaa, or XIba are advantageously separated by common purification methods known to the skilled person in the art before proceeding in the reaction sequence.

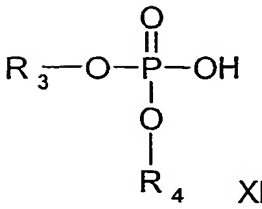
The separation, isolation, and purification methods of the present invention include, but are not limited to chromatography, such as adsorption chromatography (including column chromatography and simulated moving bed (SMB)), crystallisation, or distillation. The separation, isolation, and purification methods may be used subsequently and in combination. Column chromatography, useful for the separation of vitamin D analogues of the present invention is well known to those skilled in the art of pharmaceutical chemistry. The technique employs a column packed with a stationary phase, for example silica, such as pretreated silica onto which sample to be separated is loaded. The sample is then eluted with a suitable eluent. Elution can be isocratic or so-called solvent programmed (gradient), wherein the composition of the eluent is varied regularly (e.g. linearly) or irregularly (e.g. stepwise over time. Pretreated silica gel, well known to a person skilled in the art of chromatography, is a suitable stationary phase. Elution with 5% (v:v) ethyl acetate in hexane or heptane followed by neat ethyl acetate is but one example of an elution program that produces the desired separation. Other suitable eluents will be deduced by the skilled person through routine methods of development, e.g. by using mixtures of heptane and ethylacetate of suitable polarity.

For the chromatography steps, any combination of stationary phase (packing) and eluent that is capable of resolving the mixtures, e.g. if C-24 epimers, can be used. Such combinations can be readily determined by the skilled person by routine experimentation.

The Horner-Emmons reagents of general structure VII can be synthesized by various synthetic approaches, ranging from the direct Arbuzov reaction of trisubstituted phosphites, e.g. trialkylphosphites, such as triethylphosphite or trimethylphosphate, with 2-halo-1-cyclopropylethanone, such as 2-chloro-1-cyclopropylethanone or 2-bromo-1-cyclopropylethanone [B.A. Arbuzov, Pure Appl. Chem. 1964, 9, 307] to methods using organometallic reagents (see for example references 5 (a)-(k) in [B. Corbel et al., Synth. Communications, 1996, 26(13), 2561-2568]). Other methods of preparation include the Michaelis-Becker process [G. Sturtz, Bull. Soc. Chim. Fr., 1964, 2333] and the use of masked carbonyl compounds (see for example references 8 (a)-(k) in [B. Corbel et al., Synth. Communications, 1996, 26(13), 2561-2568]. A safe and economical procedure for the preparation of β-keto phosphonates is based on the acylation of magnesium enolate derivative of trialkylphosphonoacetate using magnesium chloride-triethylamine followed by decarboxylation [D.Y. Kim, Synth. Commun. 1996, 26(13), 2487-2496; B. Corbel et al., Synth. Commun., 1996, 26(13), 2561-2568]. Another approach is based on the reactions of α-halophosphonates with esters promoted by a soluble Co(0) complex or by magnesium metal [F. Orsini, Synthesis, 2002, 12, 1683-1688]. Many other procedures are described in the literature and can for example be found in references cited in the above articles, e.g. by D.Y. Kim et al. and by F. Orsini et al..

The Wittig-Horner reaction is usually performed by mixing a compound of general structure IXX, XXII, IIIa, IIIb, VIa and/or VIb, XIIIa, XIIIb, XVa and/or XVb with a phosphonate and a base in an appropriate solvent. The addition of reagents may be in either order, though the addition of the base as the last reagent to the stirred mixture can be advantageously depending on the base used.

Preferably, the phosphonates of the general structure VII include groups R_3 and/or R_4, which render the corresponding phosphate esters XII water soluble, as this will allow the removal of the phosphate esters XII by aqueous extraction from the reaction mixture.



XII

For example those groups of R_3 and/or R_4 of compounds VII or XII are advantageous, which result in a water solubility for compounds of general structure XII of at least 0.1mg/ml at pH 9.5 and 20°C, such as at least 0.5mg/ml at pH 9.5 and 20°C, such as at least 1mg/ml at pH 9.5 and 20°C, such as at least 5mg/ml at pH 9.5 and 20°C, such as at least 10mg/ml at pH 9.5 and 20°C.

In a another embodiment of the invention, phosphonates of general structure VII are preferred, where the water solubility of the corresponding phosphonic acid XII is equal or higher in comparison to the solubility of phosphonic acid XII where R_3 and R_4 are ethyl.

Appropriate solvents for the Wittig-Horner reaction include hydrocarbons, such as xylenes, toluene, hexanes, heptanes, cyclohexane, and ethers, such as *tert*-butyl methyl ether, diethyl ether, 1,4-dioxane, diethoxymethane, 1,2-dimethoxyethane, or tetrahydrofuran, and other solvents such as acetonitrile, 2-methyltetrahydrofuran, diglyme, monoglyme, NMP, DMF, DMSO, or acetates, such as ethyl acetate or 2-propyl acetate, or halogenated solvents such as dichloromethane, chlorobenzene, or water, or mixtures of said solvents.

In a preferred embodiment of the invention the reaction is carried out under phase transfer conditions using a mixture of water and a water-immiscible solvent, such as toluene or xylene with a suitable phase transfer catalyst, such as a tetraalkylammonium salt, e.g. a tetrabutylammonium hydroxide, halide, or hydrogensulfate, such as tetrabutylammonium bromide or chloride, or tetrabutylammonium hydrogensulfate.

Suitable bases for the Wittig-Horner reaction include hydroxides, such as tetraalkylammonium hydroxides, e.g. tetrabutylammoniumhydroxide, or alkalimetalhydroxides, such as sodium hydroxide, potassium hydroxide, or group 2 element hydroxides, such as $Mg(OH)_2$, including aqueous solutions of such hydroxides. Other suitable bases include, depending on the reaction conditions and solvents used, sodium hexamethyldisilazane (NaHMDS) or hydrides, such as sodium or calcium hydride, or alkoxides, such as sodium ethoxide, potassium *tert*-butoxide, or lithium *tert*-butoxide.

The reaction temperature for the Wittig-Horner reactions will depend on the reaction conditions and solvents used. Typically for the reaction of compounds of general structure VIa and/or VIb, or XVa and/or XVb, reaction temperatures above 50°C should be avoided. Suitable reaction temperature for the Wittig-Horner reaction of VIa and/or VIb, or XVa and/or XVb, are in the range of -80°C to 50°C, such as -50°C to 50°C, such as -30°C to 50°C, such as -15°C to 40°C, such as -5°C to 35°C, such as 0°C to 35°C, such as 5°C to 30°C, such as 10°C to 30°C, such as 15°C to 30°C, such as 10°C to 25°C, such as 5°C to 20°C. Suitable reaction temperature for the Wittig-Horner reaction of IXX, XXII, IIIa, IIIb, XIIIa, or XIIIb are in the range of -80°C to 150°C, such as -50°C to 150°C, -40°C to 120°C, such as -30°C to 100°C, -20°C to 80°C, such as -15°C to 60°C, such as -10°C to 50°C such as -5°C to 40°C, such as 0°C to 35°C, such as 5°C to 30°C, such as 10°C to 30°C, such as 15°C to 30°C, such as 10°C to 25°C, such as 5°C to 20°C.

The phosphonate VII or XXIIIb is usually used in an equimolar amount or in molar excess with regard to the aldehydes, such as 10% excess, or 30 % excess, or 50 % excess, or 65 % excess, or 70 % excess, or 80 % excess, or 90 % excess, or 100 % excess, or 150 % excess, or 200 % excess, or 300% excess.

The base is usually used equimolar or in molar excess with regard to the phosphonate VII or XXIIIb, such as 10% excess, or 30 % excess, or 50 % excess, or 65 % excess, or 70 % excess, or 80 % excess, or 90 % excess, or 100 % excess, or 150 % excess, or 200 % excess, or 300 % excess, or 350 % excess, or 400 % excess, or 425 % excess, or 450 % excess, or 500 % excess.

The optimal reaction conditions for the Wittig-Horner reaction, such as the solvents, bases, temperature, work-up procedures, stoichiometries, or the reaction times will depend on the starting compounds, e.g. the groups R_1 and/or R_2 in the aldehydes of general structure IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, or XVb, and the group R_6 of the aldehydes XXII, and the phosphonates VII and XXIIIb, e.g. the groups R_3 and R_4.

The stereoselectivity (trans-selectivity) of the reaction may be controlled by the reaction conditions and the choice of the phosphonate VII and XXIIIb (groups R_3 and R_4).

The oxidation of the compounds of general structure XXIa, wherein R_5 is hydrogen and R_6 is hydrogen or preferably a hydroxy protecting group, such as *tert*-butyldimethylsilyl, to a compound of general structure XXII may for example be performed with pyridinium dichromate (PDC), Dess-Martin reagent, pyridinium chlorochromate (PCC), *N*-methylmorpholine *N*-oxide (NMO), such as *N*-methylmorpholine *N*-oxide on silica, tetrapropylammonium perrhutenate, for example in dichloromethane.

The Wittig reagent XXIIIa can be prepared according to the methods described in Chemical Reviews, 1995, Vol. 95, No.6 and J. Org. Chem. 2002, 67, 1580-1887. The Wittig Horner raegent XXIIIb may for example be prepared from compound 6 disclosed in J. Org. Chem. 2002, 67, 1580-1887, followed by reaction with suitable halogenating agent, such as thionyl chloride, and reaction of the resulting halogenide or chloride with triethyl phosphate in a Michaelis Arbuzov reaction, such as by heating with triethylphosphite.

Coupling conditions of coupling compound XXII with XXIIIa or XXIIIb can also be found in Chemical Reviews, 1995, Vol. 95, No.6, or J. Org. Chem. 2002, 67, 1580-1887, and references cited therein. A suitable base is for example an lithiumalklyl derivative, such as sec-butyl lithium or n-butyllithium.

Hydroxylation, such as hydroxylation of the compound of general structure XIVa can be achieved with a suitable hydroxylating agent, for example by a selenite mediated allylic hydroxylation, such as under the conditions developed by Hesse, e.g. with selene dioxide (SeO_2), such as with SeO_2 and *N*-methylmorpholine *N*-oxide in refluxing methanol and/or dichloromethane) [J. Org. Chem. 1986, 51, 1637] or as described in Tetrahedron Vol. 43. No.20, 4609-4619, 1987 or in WO87/00834. The undesired hydroxy epimer formed during hydroxylation may be removed by the general separation and chromatography methods described herein.

Calicpotriol hydrate can be obtained by crystallisation of calcipotriol from aqueous solvents, such as for example by methods described in WO 94/15912.

EXAMPLES

General:

All chemicals, unless otherwise noted were from commercial sources. For ^1H nuclear magnetic resonance (NMR) spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified; for deuteriochloroform solutions relative to internal tetramethylsilane (δ = 0.00) or chloroform (δ = 7.26) or deuteriochloroform (δ = 76.81 for ^{13}C NMR) standard. The value of a multiplet, either defined (doublet (d), triplet (t), quartet (q)) or not (m) at the approximate mid point is given unless a range is quoted. All organic solvents used were of technical grade. Chromatography was performed on silica gel optionally using the flash technique. Preferably the silica was from Merck KGaA Germany: LiChroprep® Si60 (15-25µm). Appropriate mixtures of ethyl acetate, dichloromethane, methanol, hexane and petroleum ether (40-60) or heptane were used as eluents unless otherwise noted.

Experimental conditions regarding melting points, elemental analysis, UV-VIS absorption, ^{1}H NMR, and mass spectrometry data were, unless otherwise noted, as described by M. J. Calverley in Tetrahedron, Vol. 43, No. 20, p. 4614-15, 1987.

Preparation 1:

(2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester

Compound VII (R_3, R_4 = ethyl)

Cyclopropane carbonyl chloride (ALDRICH) (125g) was added slowly to a mixture of anhydrous magnesium chloride (102 g), triethylphosphonoacetate (219 g), and triethyl amine (310 g) in toluene (1600 ml) with stirring keeping the temperature below 25°C. The mixture was stirred for another 30 minutes followed by the cautious addition of first water (950 ml), followed by a mixture of concentrated hydrochloric acid (250 ml) and water (350 ml), keeping the temperature below 25°C. The organic phase was separated, washed with an aqueous sodium chloride (400g NaCl in 1200 ml water) and then washed with water (1600 ml). The organic phase was then concentrated *in vacuo* to the lowest possible volume to give 3-cyclopropyl-2-(diethoxyphosphoryl)-3-oxo-propionic acid ethyl ester as an oil. Water was added (40 ml) to the the oil and this mixture was refluxed for approximately 3 hours. More water (2000 ml) was added to the reaction mixture and the title compound was extracted with methylene chloride. The solvents were removed *in vacuo* to give the title compound as oil. The ^{31}P NMR, and mass spectrometry data were found to be in full accordance with structure. ^{1}H NMR ($CDCl_3$):
4.16 (m,4H), 3.21 (d,2H), 2.20 (m,1H), 1.34 (t,6H), 1.11 (m,2H), 0.98 (m,2H) ppm.

Preparation 2:

(2-cyclopropyl-2-oxoethyl)phosphonic acid dimethyl ester

Compound VII (R_3, R_4 = methyl)

The same procedure as in Preparation 1 may be used, but using trimethylphosphonoacetate instead of triethylphosphonoacetate. The ^{31}P NMR, and mass spectrometry data were found to be in full accordance with the structure. ^{1}H NMR ($CDCl_3$): 3.80 (d,6H), 3.22 (d,2H), 2.17 (m,1H), 1.11 (m,2H),0.98 (m,2H) ppm.

Example 1:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1, R_2 = *tert*-butyldimethylsilyl)

A mixture of (2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester (compound VII / R_3, R_4 = ethyl) (46.0 g, 209mmol), 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-

formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1, R_2 = *tert*-butyldimethylsilyl) prepared according to M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 (72.2 g, 126mmol), toluene (1100 ml), water (122 ml), tetrabutyl ammonium bromide (3.13 g), and sodium hydroxide solution 27.7% (128.0 g) was stirred at 30°C for approximately one hour followed by stirring at ambient temperature (15-25°C) overnight. When the reaction was judged to be complete as checked by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270nm, hexane/ethylacetate 100:2 (v:v)], water was added (500 ml). The pH of the reaction mixture was adjusted to pH 8.5-9.5 by addition of phosphoric acid solution (ca. 20%) keeping the temperature between 20-25°C. The organic phase was separated followed by the addition of hexane (200ml) and methanol (170 ml). The organic phase was once washed with a mixture of water (670 ml), saturated aqueous sodium chloride (120 ml), and saturated aqueous sodium hydrogen carbonate (20 ml). The organic solvents were removed *in vacuo* and the remainder was dissolved in a mixture of methanol (500 ml) and hexane (580 ml), and the solution was then washed with water (400 ml). The organic solvents were again removed *in vacuo* and the remainder was crystallised from *tert*-butyl methyl ether/methanol. The crystals were filtered off, washed twice with methanol and dried under vacuum to give the title compound 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (65.2 g, 102 mmol). The melting point, elemental analysis, UV-VIS absorption, and mass spectrometry data were found to be in full accordance with the structure as described earlier by M. J. Calverley in Tetrahedron, Vol. 43, No. 20, p. 4616, 1987 for compound 17. ^{13}C NMR ($CDCl_3$): 200.4, 153.4, 151.8, 142.5, 135.5, 128.1, 121.4, 116.5, 106.5, 70.0, 67.0, 56.0, 55.3, 46.0, 43.7, 40.2, 40.1, 36.4, 28.7, 27.4, 25.7, 25.6, 23.2, 22.1, 19.3, 18.5, 18.1, 17.9, 12.1, 10.7, 10.7, -5.0, -5.0, -5.1, -5.1 ppm.

Example 1A:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1, R_2 = *tert*-butyldimethylsilyl)

To a solution of (2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester (compound VII / R_3, R_4 = ethyl) (1.51 g) and THF (16 ml) was added NaHMDS (sodium hexamethyldisilazane) (3.2ml, 2M in THF) over 10 min below -50 °C and stirred additionally for 3-4 hr followed by addition of a solution of 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa/ R_1, R_2 = *tert*-butyldimethylsilyl) (2 g) in THF (3 ml) below -50 °C. The

reaction was stirred additionally for 2 hr below -50 °C and then 2 hr at -25 °C before the temperature was elevated to room temperature overnight. The reaction was checked for completion by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270 nm, hexane/ethylacetate 100:2 (v:v)].

Example 1B:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1, R_2 = *tert*-butyldimethylsilyl)

To a solution of (2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester (compound VII / R_3, R_4 = ethyl) (1,51 g) and THF (16 ml) was added NaH (265 mg) over 3 min below -50 °C and stirred additionally for 2-3 hr followed by addition of a solution of 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1, R_2 = *tert*-butyldimethylsilyl) (2.1 g) in THF (3 ml) below -50 °C . The reaction was stirred further for 2 hr below -50 °C and then 3.5 hr at -25 °C before the temperature was elevated to room temperature overnight. The reaction was checked for completion by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270 nm, hexane/ethylacetate 100:2 (v:v)].

Example 1C:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1, R_2 = *tert*-butyldimethylsilyl)

To a solution of (2-cyclopropyl-2-oxoethyl)phosphonic acid dimethyl ester (compound VII / R_3, R_4 = methyl) (1,51 g) and THF (16 ml) was added NaHMDS (3.2ml, 2M in THF) over 10 min below -50 °C and stirred further 4 hr followed by addition of a solution of 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1, R_2 = *tert*-butyldimethylsilyl) (2 g) in THF (3 ml). The reaction was stirred additionally for 2 hr below -50 °C and then 2 hr at -25 °C before the temperature was elevated to room temperature overnight. The reaction was checked for completion by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270 nm, hexane/ethylacetate 100:2 (v:v)].

Example 1D:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1, R_2 = *tert*-butyldimethylsilyl)

A mixture of (2-cyclopropyl-2-oxoethyl)phosphonic acid dimethyl ester (compound VII / R_3, R_4 = methyl) (1.08 g), 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1, R_2 = *tert*-butyldimethylsilyl) (1.28 g), toluene (15 ml), water (1.2 ml), tetrabutyl ammonium bromide (49 mg), and sodium hydroxide solution 27.7% (1.54 ml) was stirred at 33°C overnight. The reaction was checked for completion by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270 nm, hexane/ethylacetate 100:2 (v:v)].

Preparation 3:

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

Compound IIIb (R_1, R_2 = *tert*-butyldimethylsilyl).

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1, R_2 = *tert*-butyldimethylsilyl) may be photoisomerised in toluene using anthracene as triplet sensitizer followed by chromatography of the crude product to give the title compound. ^{13}C NMR ($CDCl_3$): 204.8, 148.1, 139.7, 135.4, 122.7, 118.2, 111.1, 71.9, 67.3, 55.4, 51.3, 49.6, 46.0, 45.9, 44.6, 40.1, 28.6, 26.3, 25.7, 25.6, 23.1, 22.3, 18.0, 18.0, 13.4, 12.2, -4.9, -5.0, -5.3 ppm.

Example 2:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

Compound Vb (R_1, R_2 = *tert*-butyldimethylsilyl).

The same procedure as in Example 1 may be used, using 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb / R_1, R_2 = *tert*-butyldimethylsilyl) as the starting material, except that the product may be purified by chromatography instead of crystallisation to give the title compound. ^1H NMR ($CDCl_3$): 6.78 (dd,1H), 6.24 (d,1H), 6.16 (d,1H), 6.02 (d,1H), 5.19 (d,1H), 4.87 (d,1H), 4.38 (m,1H), 4.20 (m,1H), 2.85 (dd,1H), 2.46 (dd,1H), 2.38 – 1.20 (m,16H), 1.13 (d,3H), 1.08 (m,2H), 0.91 (m,2H), 0.89 (s,18H), 0.59 (s,3H), 0.07 (m,12H) ppm.

Preparation 4:

1(S),3(R)-dihydroxy-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene IIIb (R_1, R_2 = hydrogen).

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb / R_1, R_2 = *tert*-butyldimethylsilyl) from Preparation 3 may be deprotected with aqueous hydrofluoric acid (40%) to give the title compound IIIb (R_1, R_2 = hydrogen) compound. ^1H NMR ($CDCl_3$): 9.58 (d,1H), 6.37 (d,1H), 6.04 (d,1H), 5.33 (s,1H), 4.99 (s,1H) , 4.43 (m,1H), 4.23 (m,1H), 2.85 (dd,1H), 2.60 (dd,2H), 2.44 – 2.26 (m,2H), 2.10 – 1.30 (m,14H), 1.14 (d,3H), 0.60 (s,3H) ppm.

Example 4:

1(S),3(R)-dihydroxy-20(R)-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene

Compound Vb (R_1, R_2 = hydrogen)

The same procedure as in Example 1 may be used, using 1(S),3(R)-dihydroxy-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb / R_1, R_2 = hydrogen) from Preparation IV as the starting material, except that the product may be purified by chromatography instead of crystallisation to give the title compound. ^{13}C NMR ($CDCl_3$): 200.8, 152.1, 147.7, 142.2, 133.5, 128.3, 124.7, 117.4, 111.8, 70.7, 66.8, 56.1, 55.5, 46.1, 45.2, 42.8, 40.3, 40.2, 29.0, 27.4, 23.5, 22.3, 19.5, 18.7, 12.3, 11.0 ppm.

Preparation 5:

1(S),3(R)-bis(trimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

Compound IIIb (R_1, R_2 = trimethylsilyl).

1(S),3(R)-dihydroxy-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb / R_1, R_2 = hydrogen) from Preparation 4 may be reacted with trimethylsilyl chloride in the presence of triethylamine in dichloromethane. The obtained raw product may be purified by chromatography to give the pure title compound. ^{13}C NMR ($CDCl_3$): 204.7, 147.8, 140.1, 135.2, 122.9, 118.1, 111.4, 71.4, 67.0, 55.4, 51.3, 49.5, 46.0, 45.7, 44.6, 40.1, 28.7, 26.3, 23.2, 22.3, 13.4, 12.2, 0.0, -0.1 ppm.

Preparation 6:

1(S)-*tert*-butyldimethylsilyloxy-3(R)-hydroxy-20(S)-formyl-9,10-secopregna-5(E),7(*E*),10(19)-triene

IIIa (R_1 = hydrogen, R_2 = *tert*-butyldimethylsilyl), and

1(S)-hydroxy-3(R)-*tert*-butyldimethylsilyloxy-20(S)-formyl-9,10-secopregna-5(E),7(*E*),10(19)-triene

IIIa (R_1 = *tert*-butyldimethylsilyl, R_2 = hydrogen).

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1 , R_2 = *tert*-butyldimethylsilyl) may be

partially deprotected with tetrabutylammonium fluoride to give a mixture of the title compounds and the unprotected derivative IIIa (R_1, R_2 = hydrogen). The compounds of the mixture may be separated by column chromatography to give pure fractions of the title compounds IIIa (R_1 = hydrogen, R_2 = *tert*-butyldimethylsilyl), ^{1}H NMR ($CDCl_3$): 9.59 (d,1H), 6.50 (d,1H), 5.86 (d,1H), 5.01 (s,1H), 4.94 (s,1H), 4.48 (t,1H), 4.24 (m,1H), 2.88 (dd,1H), 2.62 (dd,1H), 2.50 – 2.30 (m,2H), 2.11 – 1.30 (m,14H), 1.13 (d,3H), 0.88 (s,9H), 0.60 (s,3H), 0.06 (s,3H), 0.04 (s,3H) ppm; and IIIa (R_1 = *tert*-butyldimethylsilyl, R_2 = hydrogen), ^{1}H NMR ($CDCl_3$): 9.59 (d,1H), 6.49 (d,1H), 5.86 (d,1H), 5.07 (s,1H), 4.95 (s,1H), 4.49 (m,1H), 4.20 (m,1H), 2.87 (dd,1H), 2.52 (dd,1H), 2.45 – 2.30 (m,2H), 2.12 – 1.31 (m,14H), 1.13 (d,3H), 0.86 (s,9H), 0.59 (s,3H), 0.06 (s,6H) ppm.

Example 5:

1(S)-*tert*-butyldimethylsilyl-3(R)-hydroxy-20(R)-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1 = hydrogen, R_2 = *tert*-butyldimethylsilyl)

The same procedure as in Example 1 may be used, using 1(S)-*tert*-butyldimethylsilyl-3(R)-hydroxy-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1 = hydrogen, R_2 = *tert*-butyldimethylsilyl) from Preparation 6 as the starting material, except that the product may be purified by chromatography instead of crystallisation gave the title compound. ^{1}H NMR ($CDCl_3$): 6.75 (dd,1H), 6.50 (d,1H), 6.14 (d,1H), 5.84 (d,1H), 5.00 (s,1H), 4.92 (s,1H), 4.47 (t,1H), 4.22 (m,1H), 2.85 (dd,1H), 2.62 (dd,1H), 2.43 (dd,1H), 2.29 (m,1H), 2.15 – 1.15 (m,15H), 1.11 (d,3H), 1.06 (m,2H), 0.87 (s,9H), 0.86 (m,2H), 0.59 (s,3H), 0.06 (s,3H), 0.04 (s,3H) ppm.

Example 6:

1(S)-hydroxy-3(R)-*tert*-butyldimethylsilyl-20(R)-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R_1 = *tert*-butyldimethylsilyl, R_2 = hydrogen)

The same procedure as in Example 1 may be used, using 1(S)-hydroxy-3(R)-*tert*-butyldimethylsilyl-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R_1 = *tert*-butyldimethylsilyl, R2 = hydrogen) from Preparation 6 as the starting material, except that the product may be purified by chromatography instead of crystallisation gave the title compound. ^{1}H NMR ($CDCl_3$): 6.76 (dd,1H), 6.49 (d,1H), 6.14 (d,1H), 5.85 (d,1H), 5.06 (s,1H), 4.95 (s,1H), 4.49 (m,1H), 4.19 (m,1H), 2.86 (dd,1H), 2.52 (dd,1H), 2.45 – 1.20 (m,17H), 1.12 (d,3H), 1.07 (m,2H), 0.88 (m,2H), 0.86 (s,9H), 0.59 (s,3H), 0.06 (s,6H) ppm.

Example 7:

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene SO_2-adducts

Compound VIIIa and VIIIb (R_1, R_2 = *tert*-butyldimethylsilyl)

A mixture of (2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester (Compound VII R_3, R_4 = ethyl) (30 g), 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene SO_2-adducts (compounds VIa and VIb / R_1, R_2 = *tert*-butyldimethylsilyl) (34.8 g) (compounds 14a and 14 b described in M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987), toluene (350 ml), water (35 ml), tetrabutyl ammonium bromide (1.01 g), and sodium hydroxide solution 27.7% (35 ml) was stirred at 33°C for approximately 1.5 hour. When the reaction was judged to be complete as checked by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection with MS, hexane/ethylacetate 100:2 (v:v)], water was added (160 ml). The pH of the reaction mixture was adjusted to pH 8.5-9.5 by addition of phosphoric acid solution (ca. 20%) keeping the temperature between 20-25°C. The organic phase was separated followed by the addition of MTBE (90ml), water (600 ml), saturated aqueous sodium chloride (60 ml), and saturated aqueous sodium hydrogen carbonate (10 ml). The toluene phase was separated and the solvent removed *in vacuo* without heating (preferably below 30°C) to give the two epimeric SO_2-adducts VIIIa and VIIIb / R_1, R_2 = *tert*-butyldimethylsilyl as a solid mixture predominantly containing VIIIa as checked by TLC. The two epimeric SO_2-adducts VIIIa and VIIIb could be separated by chromatography. Crystalline VIIIa could be furthermore obtained by tituration of the solid mixture with methanol. ^1H NMR ($CDCl_3$) VIIIa/ R_1, R_2 = *tert*-butyldimethylsilyl = 6.73 (dd,1H), 6.14 (d,1H), 4.69 (d,1H), 4.62 (d,1H), 4.35 (s,1H), 4.17 (m,1H), 3.92 (d,1H), 3.58 (d,1H), 2.61 (m,1H), 2.29 (m,1H), 2.2 – 1.2 (m,16H), 1.11 (d,3H), 1.05 (m,2H), 0.90 (m,2H), 0.87 (s,9H), 0.85 (s,9H), 0.68 (s,3H), 0.06 (s,3H), 0.05 (s,3H), 0.04 (s,3H), 0.02 (s,3H) ppm.

Example 8:

20(R),3(R)-(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene SO_2-adducts

Compound XVIa and XVIb (R_1 = *tert*-butyldimethylsilyl)

The same procedure as in Example 7 using 3(R)-(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene SO_2-adducts (mixture of the two epimeric SO_2-adducts XVa and compound XVb) as the starting material giving the two epimeric SO_2-adducts XVIa and XVIb / R_1 = *tert*-butyldimethylsilyl as a solid mixture

predominantly containing XVIa as checked by TLC. The two epimeric SO_2-adducts XVIa and XVIb could be separated by chromatography. Crystalline XVIa could be furthermore obtained by tituration of the solid mixture with methanol. ^{13}C-NMR ($CDCl_3$) (mixture of the two epimeric SO_2-adducts XVIa and XVIb / R_1 = *tert*-butyldimethylsilyl) 200.3, 151.6, 151.4, 149.8, 149.2, 130.5, 130.1, 128.3, 128.1, 126.6, 126.3, 110.5, 110.0, 67.4, 66.7, 66.6, 66.3, 58.0, 57.9, 55.8, 55.6, 55.3, 55.2, 46.3, 45.5, 39.9, 39.7, 34.4, 34.1, 33.9, 31.4, 30.8, 30.5, 29.6, 29.1, 27.3, 27.1, 26.7, 25.6, 25.1, 24.4, 24.1, 23.6, 23.2, 22.4, 21.9, 21.9, 19.4, 19.3, 18.6, 18.4, 17.9, 17.9, 13.9, 12.2, 11.9, 10.8, -5.0 ppm.

Example 9:

20(R),3(R)-(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound XIVa (R_1= *tert*-butyldimethylsilyl)

A mixture of ETH655 (2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester (compound VII / R_3, R_4 = ethyl) (22,4 g), 3(R)-(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compounds XIIIa / R_1 = *tert*-butyldimethylsilyl) (27 g) prepared according to M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987, toluene (328 ml), water (35 ml), tetrabutyl ammonium bromide (0.93 g), and sodium hydroxide solution 27.7% (38 g) was stirred at 33°C for approximately 1 hour. When the reaction was judged to be complete as checked by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270 nm, hexane/ethylacetate 100:2 (v:v)], water was added (150 ml). The pH of the reaction mixture was adjusted to pH 7.8 by addition of phosphoric acid solution (ca. 20%) keeping the temperature between 20-25°C. The organic phase was separated followed by the addition of water (2000 ml), saturated aqueous sodium chloride (36 ml), and saturated aqueous sodium hydrogen carbonate (6 ml). The organic solvents were removed *in vacuo*. ^{13}C NMR ($CDCl_3$) (compound XIVa / R_1= *tert*-butyldimethylsilyl): 200.3, 151.8, 149.8, 142.8, 136.4, 128.1, 119.7, 116.1, 107.4, 69.2, 56.1, 55.3, 45.9, 40.2, 40.0, 37.3, 35.0, 30.9, 28.7, 27.3, 25.7, 23.2, 22.0, 19.3, 18.5, 18.0, 12.2, 10.7, -4.9 ppm.

Example 10:

1-Cyclopropyl-4-(4-triethylsilanyloxy-7a-methyl-octahydro-inden-1-yl)-pent-2-en-1-one

Compound XX (R_5= triethylsilyl)

2-(7a-Methyl-4-triethylsilanyloxy-octahydro-inden-1-yl)-propionaldehyde IX (R_5 = triehtylsilyl), which was synthesised as described in *Eur.J.Org.Chem.* 2003, pp. 3889-

3895, (2 g) was added to a mixture of Li-*tert.*-butoxide (0.6 g) and (2-cyclopropyl-2-oxoethyl)phosphonic acid diethyl ester (compound VII / R_3, R_4 = ethyl) (1.62 g) in THF (50ml) at –50 °C. After complete reaction the reaction was quenched with water (50 ml) and extracted with hexane (100 ml). The organic phase was filtered through silica gel and concentrated in vacuo to give compound XX (R_5= triethylsilyl) as an clear oil (2 g). ^{1}H-NMR ($CDCL_3$): 6.74 (dd,1H), 6.12 (d,1H), 4.03 (m,1H), 2.40 – 0.80 (m,21H), 1.06 (d,3H), 0.94 (t,9H), 0.54 (q,6H) ppm.

Preparation 7:

1-Cyclopropyl-4-(4-triethylsilanyloxy-7a-methyl-octahydro-inden-1-yl)-pent-2-en-1-(S)-ol

Compound XXIa (R_5= triethylsilyl)

(1S,2R)-(-)-cis-1-amino-2-indanol (6.33 g, 0.87 eq.) was mixed with MTBE (100 ml) under a nitrogen atmosphere at 15-25°C followed by the addition of N,N-diethylaniline-borane (16.0 ml, 1.85 eq.) at that temperature. The mixture was stirred until no more evolution of hydrogen could be observed. 1-Cyclopropyl-4-(4-triethylsilanyloxy-7a-methyl-octahydro-inden-1-yl)-pent-2-en-1-one (compound XX / R_5 = triethylsilyl) from Example 10 (19.0 g) was dissolved in MTBE (80ml) at room temperature and then added dropwise to said mixture at 15-25°C over 2 hours. The mixture was stirred for ca. 10 minutes after complete addition and then quenched with saturated aqueous $NaHCO_3$ (100ml) and extracted with hexane (200ml). The organic phase was separated and washed with 1 M hydrochloric acid (4X120ml) at 0-10°C followed by washing with saturated aqueous $NaHCO_3$ (100ml) and water (50ml) giving the mixture of compound XXIa and XXIb (R_5 = triethylsilyl) in a molar ratio of 87:13 as checked by HPLC analysis. {Column LiChrosorb Si 60 5 µm 250X4mm from Merck 1ml/min flow, MS-detection, hexane/ethylacetate 90:10 (v:v): RT XXIa= ca. 9.9 min, RT XXIb= ca. 8.4 min}. ^{1}H-NMR ($CDCl_3$) XXIa / R_5=triethylsilyl: 138.0, 128.3, 76.6, 69.1, 56.2, 41.9, 40.5, 39.0, 34.4, 30.1, 27.4, 22.8, 20.0, 17.5, 17.3, 13.5, 6.7, 4.7, ppm; XXIb / R_5= triethylsilyl: 138.2, 128.4, 77.1, 69.2, 56.1, 53.0, 41.9, 40.5, 39.1, 34.4, 27.5, 22.8, 20.0, 17.5, 17.4, 13.5, 6.7, 4.8 ppm.